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(54) **Title:** CELLULAR ACCUMULATION OF PHOSPHONATE ANALOGS OF HIV PROTEASE INHIBITOR COMPOUNDS

(57) **Abstract:** Phosphonate substituted compounds with HIV protease inhibitory properties having use as therapeutics and for other industrial purposes are disclosed. The compositions inhibit 5 HIV protease activity and/or are useful therapeutically for the treatment of AIDS and other antiviral infections, as well as in assays for the detection of HIV protease.

CELLULAR ACCUMULATION OF PHOSPHONATE ANALOGS OF HIV PROTEASE INHIBITOR COMPOUNDS

This non-provisional application claims the benefit of Provisional Applications 60/375,622, filed April 26, 2002; Provisional Application No. 60/375,779 filed April 26, 2002; Provisional Application No. 60/375,834, filed April 26, 2002, and Provisional Application No. 60/375,665 filed April 26, 2002, all of which are incorporated herein by reference. Additionally, copending applications Attorney Docket Nos. 259.PC and 260.PC filed concurrently with this application are also incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

The invention relates generally to compounds with antiviral activity and more specifically with anti-HIV protease properties.

BACKGROUND OF THE INVENTION

AIDS is a major public health problem worldwide. Although drugs targeting HIV viruses are in wide use and have shown effectiveness, toxicity and development of resistant strains have limited their usefulness. Assay methods capable of determining the presence, absence or amounts of HIV viruses are of practical utility in the search for inhibitors as well as for diagnosing the presence of HIV.

Human immunodeficiency virus (HIV) infection and related disease is a major public health problem worldwide. The retrovirus human immunodeficiency virus type 1 (HIV-1), a member of the primate lentivirus family (DeClercq E (1994) *Annals of the New York Academy of Sciences*, 724:438-456; Barre-Sinoussi F (1996) *Lancet*, 348:31-35), is generally accepted to be the causative agent of acquired immunodeficiency syndrome (AIDS) Tarrago etal *FASEB Journal* 1994, 8:497-503). AIDS is the result of repeated replication of HIV-1 and a decrease in immune capacity, most prominently a fall in the number of CD4+ lymphocytes. The mature virus has a single stranded RNA genome that encodes 15 proteins (Frankel etal (1998) *Annual Review of Biochemistry*, 67:1-25; Katz etal (1994) *Annual Review of Biochemistry*, 63:133-173), including three key enzymes: (i) protease (Prt) (von der Helm K (1996) *Biological Chemistry*, 377:765-774); (ii) reverse transcriptase (RT) (Hottiger etal (1996) *Biological Chemistry Hoppe-Seyler*, 377:97-120), an enzyme unique to retroviruses; and (iii) integrase (Asante etal (1999) *Advances in Virus Research* 52:351-369; Wlodawer A (1999) *Advances in Virus Research* 52:335-350; Esposito etal (1999) *Advances in Virus Research* 52:319-333). Protease is responsible for processing the viral precursor polyproteins, integrase is responsible for the integration of the double stranded DNA form of the viral genome into host DNA and RT is the key enzyme in the replication of the viral genome. In viral replication, RT acts as both an RNA- and a DNA-dependent DNA polymerase, to convert the single stranded RNA genome into double stranded DNA. Since virally encoded Reverse Transcriptase (RT) mediates specific reactions during the natural reproduction of the virus, inhibition of HIV RT is an important therapeutic target for treatment of HIV infection and related disease.

Sequence analysis of the complete genomes from several infective and non-infective HIV-isolates has shed considerable light on the make-up of the virus and the types of molecules that are essential for its replication and maturation to an infective species. The HIV protease is essential for the processing of the viral gag and gag-pol polypeptides into mature virion proteins. L. Ratner, et al., Nature, 313:277-284 (1985); L. H. Pearl and W. R. Taylor, Nature, 329:351 (1987). HIV exhibits the same gag/pol/env organization seen in other retroviruses. L. Ratner, et al., above; S. Wain-Hobson, et al., Cell, 40:9-17 (1985); R. Sanchez-Pescador, et al., Science, 227:484-492 (1985); and M. A. Muesing, et al., Nature, 313:450-458 (1985).

A therapeutic target in AIDS involves inhibition of the viral protease (or proteinase)

that is essential for processing HIV-fusion polypeptide precursors. In HIV and several other retroviruses, the proteolytic maturation of the gag and gag/pol fusion polypeptides (a process indispensable for generation of infective viral particles) has been shown to be mediated by a protease that is, itself, encoded by the pol region of the viral genome. Y. Yoshinaka, et al., Proc. Natl. Acad. Sci. USA, 82:1618-1622 (1985); Y. Yoshinaka, et al., J. Virol., 55:870-873 (1985); Y. Yoshinaka, et al., J. Virol., 57:826-832 (1986); and K. von der Helm, Proc. Natl. Acad. Sci., USA, 74:911-915 (1977). Inhibition of the protease has been shown to inhibit the processing of the HIV p55 in mammalian cell and HIV replication in T lymphocytes. T. J. McQuade, et al., Science, 247:454 (1990).

Drugs approved in the United States for AIDS therapy include nucleoside inhibitors of RT (Smith et al (1994) *Clinical Investigator*, 17:226-243), protease inhibitors and non-nucleoside RT inhibitors (NNRTI), (Johnson et al (2000) *Advances in Internal Medicine*, 45 (1-40; Porche DJ (1999) *Nursing Clinics of North America*, 34:95-112).

The protease (or proteinase), consisting of only 99 amino acids, is among the smallest enzymes known, and its demonstrated homology to aspartyl proteases such as pepsin and renin (L. H. Pearl and W. R. Taylor, Nature, 329:351-354 (1987); and I. Katoh, et al., Nature, 329:654-656 (1987)), led to inferences regarding the three-dimensional structure and mechanism of the enzyme (L. H. Pearl and W. R. Taylor, above) that have since been borne out experimentally. Active HIV protease has been expressed in bacteria (see, e.g., P. L. Darke, et al., J. Biol. Chem., 264:2307-2312 (1989)) and chemically synthesized (J. Schneider and S. B. Kent, Cell, 54:363-368 (1988); and R. F. Nutt, et al., Proc. Natl. Acad. Sci., USA, 85:7129-7133 (1988)). Site directed mutagenesis (P. L. Darke, et al., above); and N. E. Kohl, et al., Proc. Natl. Acad. Sci., USA, 85:4686-4690 (1988)) and pepstatin inhibition (P. L. Darke, et al., J. Biol. Chem., 264:2307-2312 (1989); S. Seelmeier, et al., Proc. Natl. Acad. Sci., USA, 85:6612-6616 (1988); C.-Z. Giam and I. Borsos, J. Biol. Chem., 263:14617-14720 (1988); and J. Hansen, et al., EMBO J., 7:1785-1791 (1988)) have provided evidence for HIV protease's mechanistic function as an aspartyl protease. A study has demonstrated that the protease cleaves at the sites expected in peptides modeled after the regions actually cleaved by the enzyme in the gag and pol precursor proteins during viral maturation. P. L. Darke, et al., Biochem. Biophys. Res. Communs., 156:297-303 (1988). X-ray crystallographic analysis of the HIV-protease (M. A. Navia, et al., Nature, 337:615-620 (1989)) and a related retroviral enzyme from Rous sarcoma virus (M. Miller, et al., Nature,

337:576-579 (1989)) reveal an active site in the protease dimer that is identical to that seen in other aspartyl proteases, thus supporting the supposition (L. H. Pearl and W. R. Taylor, above) that the HIV enzyme is active as a dimer. See also Joseph A. Martin, "Recent Advances in the Design of HIV Proteinase Inhibitors," Antiviral Research, 17 (1992) 265-278.

Inhibitors of HIV protease are useful to limit the establishment and progression of infection by therapeutic administration as well as in diagnostic assays for HIV. Protease inhibitor drugs approved by the FDA include:

- saquinavir (Invirase®, Fortovase®, Hoffman-La Roche, EP-00432695 and EP-00432694)
- ritonavir (Norvir®, Abbott Laboratories)
- indinavir (Crixivan®, Merck & Co.)
- nelfinavir (Viracept®, Pfizer)
- amprenavir (Agenerase®, GlaxoSmithKline, Vertex Pharmaceuticals)
- lopinavir/ritonavir (Kaletra®, Abbott Laboratories)

Experimental protease inhibitor drugs include:

- fosamprenavir (GlaxoSmithKline, Vertex Pharmaceuticals)
- tipranavir (Boehringer Ingelheim)
- atazanavir (Bristol-Myers Squibb).

There is a need for anti-HIV therapeutic agents, i.e. drugs having improved antiviral and pharmacokinetic properties with enhanced activity against development of HIV resistance, improved oral bioavailability, greater potency and extended effective half-life *in vivo*. New HIV protease inhibitors (PI) should be active against mutant HIV strains, have distinct resistance profiles, fewer side effects, less complicated dosing schedules, and orally active. In particular, there is a need for a less onerous dosage regimen, such as one pill, once per day. Although drugs targeting HIV protease are in wide use and have shown effectiveness, particularly when employed in combination, toxicity and development of resistant strains have limited their usefulness (Palella, et al *N. Engl. J. Med.* (1998) 338:853-860; Richman, D. D. *Nature* (2001) 410:995-1001).

Combination therapy of PI and RT inhibitors has proven to be highly effective in suppressing viral replication to unquantifiable levels for a sustained period of time. Also,

combination therapy with RT and protease inhibitors have shown synergistic effects in suppressing HIV replication. Unfortunately, many patients currently fail combination therapy due to the development of drug resistance, non-compliance with complicated dosing regimens, pharmacokinetic interactions, toxicity, and lack of potency. Therefore, there is a need for new HIV protease inhibitors that are synergistic in combination with other HIV inhibitors.

Improving the delivery of drugs and other agents to target cells and tissues has been the focus of considerable research for many years. Though many attempts have been made to develop effective methods for importing biologically active molecules into cells, both *in vivo* and *in vitro*, none has proved to be entirely satisfactory. Optimizing the association of the inhibitory drug with its intracellular target, while minimizing intercellular redistribution of the drug, e.g. to neighboring cells, is often difficult or inefficient.

Most agents currently administered to a patient parenterally are not targeted, resulting in systemic delivery of the agent to cells and tissues of the body where it is unnecessary, and often undesirable. This may result in adverse drug side effects, and often limits the dose of a drug (e.g., cytotoxic agents and other anti-cancer or anti-viral drugs) that can be administered. By comparison, although oral administration of drugs is generally recognized as a convenient and economical method of administration, oral administration can result in either (a) uptake of the drug through the cellular and tissue barriers, e.g. blood/brain, epithelial, cell membrane, resulting in undesirable systemic distribution, or (b) temporary residence of the drug within the gastrointestinal tract. Accordingly, a major goal has been to develop methods for specifically targeting agents to cells and tissues. Benefits of such treatment includes avoiding the general physiological effects of inappropriate delivery of such agents to other cells and tissues, such as uninfected cells. Intracellular targeting may be achieved by methods and compositions which allow accumulation or retention of biologically active agents inside cells.

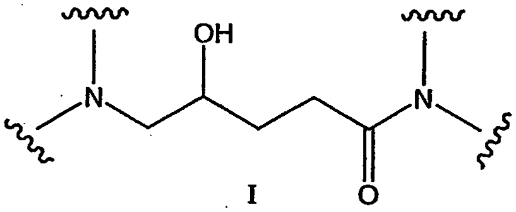
SUMMARY OF THE INVENTION

The present invention provides novel compounds with HIV protease activity, i.e. novel human retroviral protease inhibitors. Therefore, the compounds of the invention may inhibit retroviral proteases and thus inhibit the replication of the virus. They are useful for treating human patients infected with a human retrovirus, such as human immunodeficiency virus (strains of HIV-1 or HIV-2) or human T-cell leukemia viruses (HTLV-I or HTLV-II) which results in acquired immunodeficiency syndrome (AIDS) and/or related diseases. The present invention includes novel phosphonate HIV protease inhibitor (PI) compounds and phosphonate analogs of known approved and experimental protease inhibitors. The compounds of the invention optionally provide cellular accumulation as set forth below.

The present invention relates generally to the accumulation or retention of therapeutic compounds inside cells. The invention is more particularly related to attaining high concentrations of phosphonate-containing molecules in HIV infected cells. Intracellular targeting may be achieved by methods and compositions which allow accumulation or retention of biologically active agents inside cells. Such effective targeting may be applicable to a variety of therapeutic formulations and procedures.

Compositions of the invention include new PI compounds having at least one phosphonate group. The invention includes all known approved and experimental protease inhibitors with at least one phosphonate group.

In one aspect, the invention includes compounds having Formulas I, II, III, IV, V, VI, VII and VIIIa-d: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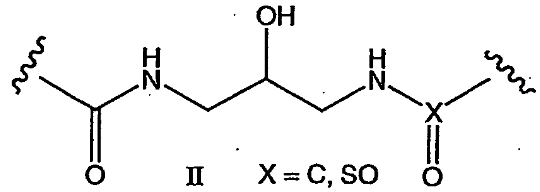
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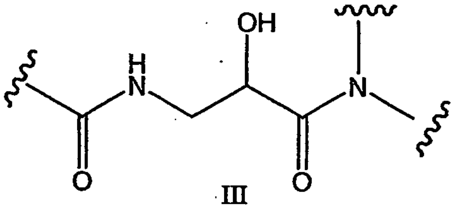
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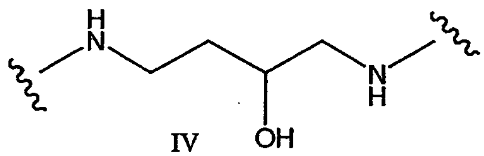
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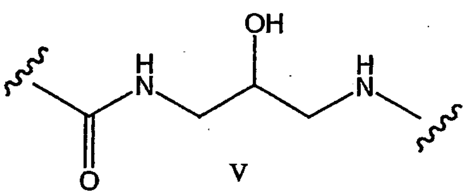
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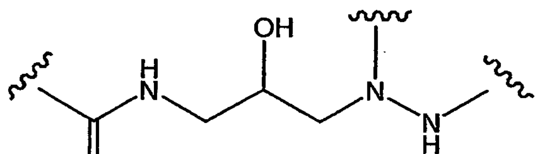
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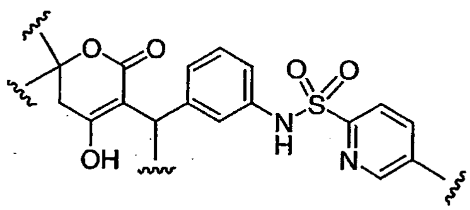
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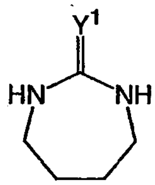
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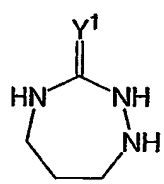
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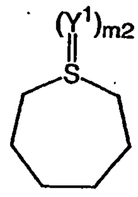
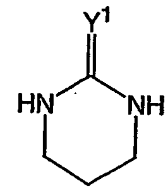
 VIIIc and  VIIId;

where a wavy line indicates the other structural moieties of the compounds.

Formulas I- VIII are substituted with one or more covalently attached groups, including at least one phosphonate group. Formulas I-VIII are "scaffolds", i.e. substructures which are common to the specific compounds encompassed therein.

Another aspect of the invention provides a pharmaceutical combination comprising an effective amount of a compound selected from Formulas I-VIII and a second compound having anti-HIV properties.

Another aspect of the invention provides a method for the treatment or prevention of the symptoms or effects of an HIV infection in an infected animal which comprises administering to, i.e. treating, said animal with a pharmaceutical combination comprising an effective amount of a compound selected from Formulas I-VIII and a second compound having anti-HIV properties.

The invention provides a pharmaceutical composition comprising an effective amount of a compound selected from Formulas I-VIII, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable diluent or carrier.

This invention pertains to a method of increasing cellular accumulation and retention of drug compounds, thus improving their therapeutic and diagnostic value.

The invention also provides a method of inhibiting HIV, comprising administering to a mammal infected with HIV (HIV positive) an amount of a compound of Formulas I-VIII, effective to inhibit the growth of said HIV infected cells.

The invention also provides a compound selected from Formulas I-VIII for use in medical therapy (preferably for use in treating cancer, e.g. solid tumors), as well as the use of a compound of Formulas I-VIII for the manufacture of a medicament useful for the treatment of cancer, e.g. solid tumors.

The invention also provides processes and novel intermediates disclosed herein which are useful for preparing compounds of the invention. Some of the compounds of Formulas I-

VIII are useful to prepare other compounds of Formulas I-VIII.

In another aspect of the invention, the activity of HIV protease is inhibited by a method comprising the step of treating a sample suspected of containing HIV virus with a compound or composition of the invention.

Another aspect of the invention provides a method for inhibiting the activity of HIV protease comprising the step of contacting a sample suspected of containing HIV virus with a composition of the invention.

In other aspects, novel methods for synthesis analysis, separation, isolation, purification, characterization, and testing of the compounds of this invention are provided.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying description, structures and formulas. While the invention will be described in conjunction with the enumerated embodiments, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents, which may be included within the scope of the present invention as defined by the claims.

DEFINITIONS

Unless stated otherwise, the following terms and phrases as used herein are intended to have the following meanings:

The terms "phosphonate" and "phosphonate group" mean a functional group or moiety within a molecule that comprises at least one phosphorus-carbon bond, and at least one phosphorus-oxygen double bond. The phosphorus atom is further substituted with oxygen, sulfur, and nitrogen substituents. These substituents may be part of a prodrug moiety. As defined herein, "phosphonate" and "phosphonate group" include molecules with phosphonic acid, phosphonic monoester, phosphonic diester, phosphonamidate, phosphondiamidate and phosphonthioate functional groups.

The term "prodrug" as used herein refers to any compound that when administered to a biological system generates the drug substance, i.e. active ingredient, as a result of spontaneous chemical reaction(s), enzyme catalyzed chemical reaction(s), photolysis, and/or

metabolic chemical reaction(s). A prodrug is thus a covalently modified analog or latent form of a therapeutically-active compound.

"Pharmaceutically acceptable prodrug" refers to a compound that is metabolized in the host, for example hydrolyzed or oxidized, by either enzymatic action or by general acid or base solvolysis, to form an active ingredient. Typical examples of prodrugs of the compounds of the invention have biologically labile protecting groups on a functional moiety of the compound. Prodrugs include compounds that can be oxidized, reduced, aminated, deaminated, esterified, deesterified, alkylated, dealkylated, acylated, deacylated, phosphorylated, dephosphorylated, photolyzed, hydrolyzed, or other functional group change or conversion involving forming or breaking chemical bonds on the prodrug.

"Prodrug moiety" means a labile functional group which separates from the active inhibitory compound during metabolism, systemically, inside a cell, by hydrolysis, enzymatic cleavage, or by some other process (Bundgaard, Hans, "Design and Application of Prodrugs" in Textbook of Drug Design and Development (1991), P. Krogsgaard-Larsen and H. Bundgaard, Eds. Harwood Academic Publishers, pp. 113-191). Enzymes which are capable of an enzymatic activation mechanism with the phosphonate prodrug compounds of the invention include, but are not limited to, amidases, esterases, microbial enzymes, phospholipases, cholinesterases, and phosphases. Prodrug moieties can serve to enhance solubility, absorption and lipophilicity to optimize drug delivery, bioavailability and efficacy.

Exemplary prodrug moieties include the hydrolytically sensitive or labile acyloxymethyl esters $-CH_2OC(=O)R^9$ and acyloxymethyl carbonates $-CH_2OC(=O)OR^9$ where R^9 is C_1–C_6 alkyl, C_1–C_6 substituted alkyl, C_6–C_{20} aryl or C_6–C_{20} substituted aryl. The acyloxyalkyl ester was first used as a prodrug strategy for carboxylic acids and then applied to phosphates and phosphonates by Farquhar et al (1983) *J. Pharm. Sci.* 72: 324; also US Patent Nos. 4816570, 4968788, 5663159 and 5792756. In certain compounds of the invention, a prodrug moiety is part of a phosphonate group. Subsequently, the acyloxyalkyl ester was used to deliver phosphonic acids across cell membranes and to enhance oral bioavailability. A close variant of the acyloxyalkyl ester, the alkoxycarbonyloxyalkyl ester (carbonate), may also enhance oral bioavailability as a prodrug moiety in the compounds of the combinations of the invention. An exemplary acyloxymethyl ester is pivaloyloxymethoxy, (POM) $-CH_2OC(=O)C(CH_3)_3$. An exemplary acyloxymethyl carbonate prodrug moiety is pivaloyloxymethylcarbonate (POC) $-CH_2OC(=O)OC(CH_3)_3$.

The phosphonate group may be a phosphonate prodrug moiety. The prodrug moiety may be sensitive to hydrolysis, such as, but not limited to a pivaloyloxymethyl carbonate (POC) or POM group. Alternatively, the prodrug moiety may be sensitive to enzymatic potentiated cleavage, such as a lactate ester or a phosphonamidate-ester group.

Aryl esters of phosphorus groups, especially phenyl esters, are reported to enhance oral bioavailability (DeLambert et al (1994) *J. Med. Chem.* 37: 498). Phenyl esters containing a carboxylic ester ortho to the phosphate have also been described (Khamnei and Torrence, (1996) *J. Med. Chem.* 39:4109-4115). Benzyl esters are reported to generate the parent phosphonic acid. In some cases, substituents at the *ortho*-or *para*-position may accelerate the hydrolysis. Benzyl analogs with an acylated phenol or an alkylated phenol may generate the phenolic compound through the action of enzymes, e.g. esterases, oxidases, etc., which in turn undergoes cleavage at the benzylic C–O bond to generate the phosphoric acid and the quinone methide intermediate. Examples of this class of prodrugs are described by Mitchell et al (1992) *J. Chem. Soc. Perkin Trans. I* 2345; Brook et al WO 91/19721. Still other benzylic prodrugs have been described containing a carboxylic ester-containing group attached to the benzylic methylene (Glazier et al WO 91/19721). Thio-containing prodrugs are reported to be useful for the intracellular delivery of phosphonate drugs. These proesters contain an ethylthio group in which the thiol group is either esterified with an acyl group or combined with another thiol group to form a disulfide. Deesterification or reduction of the disulfide generates the free thio intermediate which subsequently breaks down to the phosphoric acid and episulfide (Puech et al (1993) *Antiviral Res.*, 22: 155-174; Benzaria et al (1996) *J. Med. Chem.* 39: 4958). Cyclic phosphonate esters have also been described as prodrugs of phosphorus-containing compounds (Erion et al, US Patent No. 6312662).

"Protecting group" refers to a moiety of a compound that masks or alters the properties of a functional group or the properties of the compound as a whole. The chemical substructure of a protecting group varies widely. One function of a protecting group is to serve as intermediates in the synthesis of the parental drug substance. Chemical protecting groups and strategies for protection/deprotection are well known in the art. See: "Protective Groups in Organic Chemistry", Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991. Protecting groups are often utilized to mask the reactivity of certain functional groups, to assist in the efficiency of desired chemical reactions, e.g. making and breaking chemical bonds in an ordered and planned fashion. Protection of functional groups of a compound

alters other physical properties besides the reactivity of the protected functional group, such as the polarity, lipophilicity (hydrophobicity), and other properties which can be measured by common analytical tools. Chemically protected intermediates may themselves be biologically active or inactive.

Protected compounds may also exhibit altered, and in some cases, optimized properties *in vitro* and *in vivo*, such as passage through cellular membranes and resistance to enzymatic degradation or sequestration. In this role, protected compounds with intended therapeutic effects may be referred to as prodrugs. Another function of a protecting group is to convert the parental drug into a prodrug, whereby the parental drug is released upon conversion of the prodrug *in vivo*. Because active prodrugs may be absorbed more effectively than the parental drug, prodrugs may possess greater potency *in vivo* than the parental drug. Protecting groups are removed either *in vitro,* in the instance of chemical intermediates, or *in vivo*, in the case of prodrugs. With chemical intermediates, it is not particularly important that the resulting products after deprotection, e.g. alcohols, be physiologically acceptable, although in general it is more desirable if the products are pharmacologically innocuous.

Any reference to any of the compounds of the invention also includes a reference to a physiologically acceptable salt thereof. Examples of physiologically acceptable salts of the compounds of the invention include salts derived from an appropriate base, such as an alkali metal (for example, sodium), an alkaline earth (for example, magnesium), ammonium and NX_4^+ (wherein X is C_1–C_4 alkyl). Physiologically acceptable salts of an hydrogen atom or an amino group include salts of organic carboxylic acids such as acetic, benzoic, lactic, fumaric, tartaric, maleic, malonic, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids, such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids; and inorganic acids, such as hydrochloric, sulfuric, phosphoric and sulfamic acids. Physiologically acceptable salts of a compound of an hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+ and NX_4^+ (wherein X is independently selected from H or a C_1–C_4 alkyl group).

For therapeutic use, salts of active ingredients of the compounds of the invention will be physiologically acceptable, i.e. they will be salts derived from a physiologically acceptable acid or base. However, salts of acids or bases which are not physiologically acceptable may also find use, for example, in the preparation or purification of a physiologically acceptable

compound. All salts, whether or not derived form a physiologically acceptable acid or base, are within the scope of the present invention.

"Alkyl" is C_1-C_{18} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms. Examples are methyl (Me, $-CH_3$), ethyl (Et, $-CH_2CH_3$), 1-propyl (n-Pr, n-propyl, $-CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, $-CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, $-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, $-CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, $-CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, $-C(CH_3)_3$), 1-pentyl (n-pentyl, $-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl ($-CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl ($-CH_2CH(CH_3)CH_2CH_3$), 1-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($-CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($-CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl ($-C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl ($-CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl ($-CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl ($-C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl ($-CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl ($-C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl ($-CH(CH_3)C(CH_3)_3$.

"Alkenyl" is C_2-C_{18} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, i.e. a carbon-carbon, sp^2 double bond. Examples include, but are not limited to: ethylene or vinyl ($-CH{=}CH_2$), allyl ($-CH_2CH{=}CH_2$), cyclopentenyl ($-C_5H_7$), and 5-hexenyl ($-CH_2\,CH_2CH_2CH_2CH{=}CH_2$)

"Alkynyl" is C_2-C_{18} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, i.e. a carbon-carbon, sp triple bond. Examples include, but are not limited to: acetylenic ($-C{\equiv}CH$) and propargyl ($-CH_2C{\equiv}CH$),

"Alkylene" refers to a saturated, branched or straight chain or cyclic hydrocarbon radical of 1-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. Typical alkylene radicals include, but are not limited to: methylene ($-CH_2-$) 1,2-ethyl ($-CH_2CH_2-$), 1,3-propyl ($-CH_2CH_2CH_2-$), 1,4-butyl ($-CH_2CH_2CH_2CH_2-$), and the like.

"Alkenylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical of 2-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkene. Typical alkenylene radicals include, but are not limited to: 1,2-ethylene ($-CH{=}CH-$).

"Alkynylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical of 2-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkyne. Typical alkynylene radicals include, but are not limited to: acetylene ($-C\equiv C-$), propargyl ($-CH_2C\equiv C-$), and 4-pentynyl ($-CH_2CH_2CH_2C\equiv CH-$).

"Aryl" means a monovalent aromatic hydrocarbon radical of 6-20 carbon atoms derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Typical aryl groups include, but are not limited to, radicals derived from benzene, substituted benzene, naphthalene, anthracene, biphenyl, and the like.

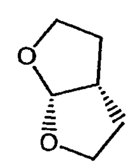
"Arylalkyl" refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with an aryl radical. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, 2-phenylethen-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, 2-naphthylethen-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. The arylalkyl group comprises 6 to 20 carbon atoms, e.g. the alkyl moiety, including alkanyl, alkenyl or alkynyl groups, of the arylalkyl group is 1 to 6 carbon atoms and the aryl moiety is 5 to 14 carbon atoms.

"Substituted alkyl", "substituted aryl", and "substituted arylalkyl" mean alkyl, aryl, and arylalkyl respectively, in which one or more hydrogen atoms are each independently replaced with a substituent. Typical substituents include, but are not limited to, -X, -R, $-O^-$, -OR, -SR, $-S^-$, $-NR_2$, $-NR_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, NC(=O)R, -C(=O)R, -C(=O)NRR $-S(=O)_2O^-$, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)O_2RR$, $-P(=O)O_2RR$ $-P(=O)(O^-)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)X, -C(S)R, -C(O)OR, $-C(O)O^-$, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, -C(NR)NRR, where each X is independently a halogen: F, Cl, Br, or I; and each R is independently -H, alkyl, aryl, heterocycle, protecting group or prodrug moiety. Alkylene, alkenylene, and alkynylene groups may also be similarly substituted.

"Heterocycle" as used herein includes by way of example and not limitation these heterocycles described in Paquette, Leo A.; "Principles of Modern Heterocyclic Chemistry" (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and *J. Am. Chem. Soc.* (1960) 82:5566.

Examples of heterocycles include by way of example and not limitation pyridyl, dihydroypyridyl, tetrahydropyridyl (piperidyl), thiazolyl, tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, bis-tetrahydrofuranyl, tetrahydropyranyl, bis-tetrahydropyranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thienyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathinyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, 1H-indazoly, purinyl, 4H-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, and isatinoyl.

One embodiment of the bis-tetrahydrofuranyl group is:



By way of example and not limitation, carbon bonded heterocycles are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Still more typically, carbon bonded heterocycles include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl.

By way of example and not limitation, nitrogen bonded heterocycles are bonded at

position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β-carboline. Still more typically, nitrogen bonded heterocycles include 1-aziridyl, 1-azetedyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

"Carbocycle" means a saturated, unsaturated or aromatic ring having 3 to 7 carbon atoms as a monocycle or 7 to 12 carbon atoms as a bicycle. Monocyclic carbocycles have 3 to 6 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles have 7 to 12 ring atoms, e.g. arranged as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system. Examples of monocyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, phenyl, spiryl and naphthyl.

"Linker" or "link" means a chemical moiety comprising a covalent bond or a chain of atoms that covalently attaches a phosphonate group to a drug. Linkers include portions of substituents A^1 and A^3 enumerated in Formula I, or substituents A_1 and A_3 enumerated in Formula II, which include moieties such as: repeating units of alkyloxy (e.g. polyethylenoxy, PEG, polymethyleneoxy) and alkylamino (e.g. polyethyleneamino, Jeffamine™); and diacid ester and amides including succinate, succinamide, diglycolate, malonate, and caproamide.

The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

"Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

"Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., Stereochemistry of Organic Compounds (1994) John Wiley & Sons, Inc., New York. Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l, D and L, or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or 1 meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

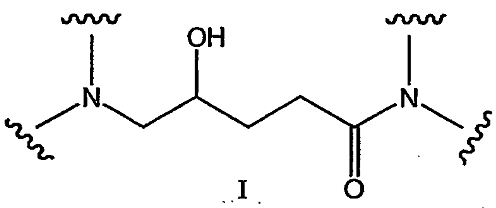
HIV Protease Inhibitor Compounds

The compounds of the invention include those with HIV protease inhibitory activity. In particular, the compounds include HIV protease inhibitors. The compounds of the inventions bear a phosphonate group, which may be a prodrug moiety.

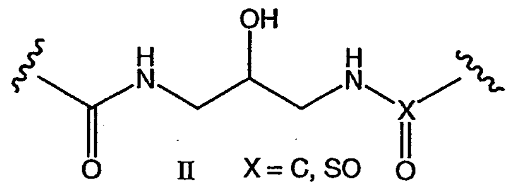
In various embodiments of the invention one identifies compounds that may fall within the generic scope of the documents cited under the definition of the terms ILPPI (Indinavir-like phosphonate protease inhibitors, Formula I); AMLPPI (Amprenavir-like phosphonate protease inhibitors, Formula II); KNILPPI (KNI-like phosphonate protease inhibitors, Formula III); RLPPI (Ritonavir-like phosphonate protease inhibitors, Formula IV); LLPPI (Lopinavir-like phosphonate protease inhibitors, Formula IV); NLPPI (Nelfinavir-like phosphonate protease inhibitors, Formula V); SLPPI (Saquinavir-like phosphonate protease inhibitors, Formula V); ATLPPI (Atanzavir-like phosphonate protease inhibitors, Formula VI); TLPPI (Tipranavir-like phosphonate protease inhibitors, Formula VII); and CCLPPI (Cyclic carbonyl-like phosphonate protease inhibitors, Formula VIIIa-d) all of which comprise a phosphonate group, e.g. a phosphonate diester, phosphonamidate-ester prodrug, or a phosphondiamidate-ester (Jiang et al, US 2002/0173490 A1).

Whenever a compound described herein is substituted with more than one of the same designated group, e.g., "R^1" or "R^{6a}", then it will be understood that the groups may be the same or different, i.e., each group is independently selected. Wavy lines indicate the site of covalent bond attachments to the adjoining groups, moieties, or atoms.

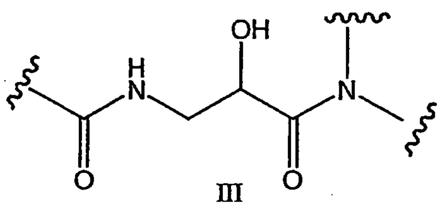
Compounds of the invention are set forth in the schemes, examples, descriptions and claims below and include the invention includes compounds having Formulas I, II, III, IV, V, VI, VII and VIIIa-d:



I



II X = C, SO



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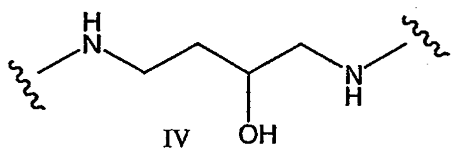
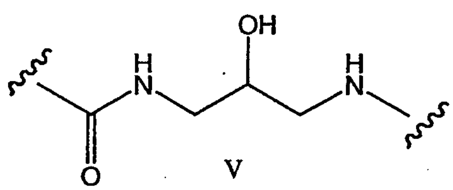
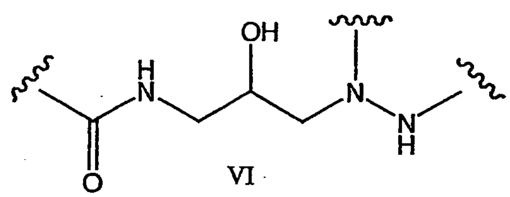


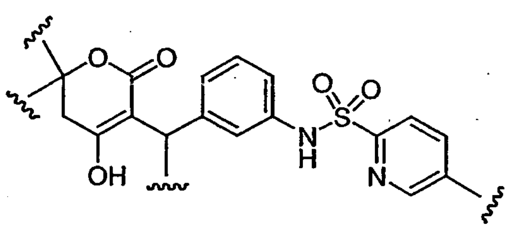
IV



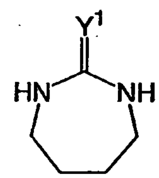
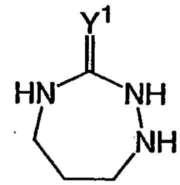
V

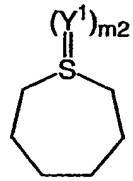
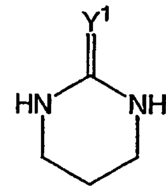


VI



VII

 VIIIa  VIIIb

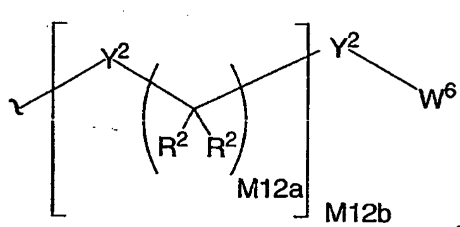
 VIIIc and  VIIId;

where a wavy line indicates the other structural moieties of the compounds.

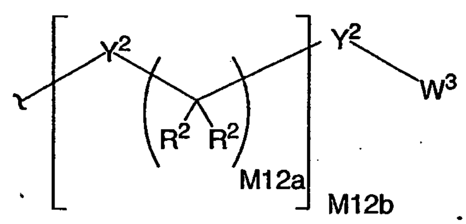
Formula I compounds have a 3-hydroxy-5-amino-pentamide core. Formula II compounds have a 2-hydroxy-1, 3-amino-propylamide or 2-hydroxy-1,3-amino-propylaminosulfone core. Formula III compounds have a 2-hydroxy-3-amino-propylamide core. Formula IV compounds have a 2-hydroxy-4-amino-butylamine core. Formula V compounds have a acylated 1,3-diaminopropane core. Formula VI compounds have a 2-hydroxy-3-diaza-propylamide core. Formula VII compounds have a sulfonamide 5,6-dihydro-4-hydroxy-2-pyrone core. Formula VIIIa-d compounds have a six or seven-membered ring, and a cyclic carbonyl, sulfhydryl, sulfoxide or sulfone core, where Y^1 is oxygen, sulfur, or substituted nitrogen and m2 is 0, 1 or 2.

Formulas I, II, III, IV, V, VI, VII and VIIIa-d are substituted with one or more covalently attached groups, including at least one phosphonate group. Formulas I, II, III, IV, V, VI, VII and VIIIa-d are substituted with one or more covalently attached A^0 groups, including simultaneous substitutions at any or all A^0. A^0 is A^1, A^2 or W^3. Compounds of Formulas I, II, III, IV, V, VI, VII and VIIIa-d include at least one A^1.

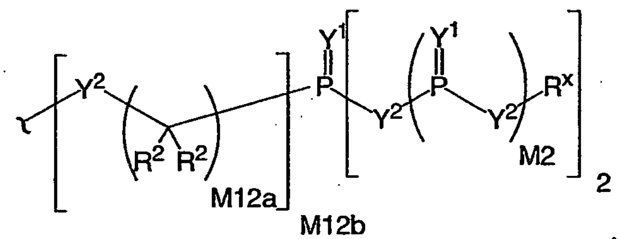
A^1 is:



A^2 is:



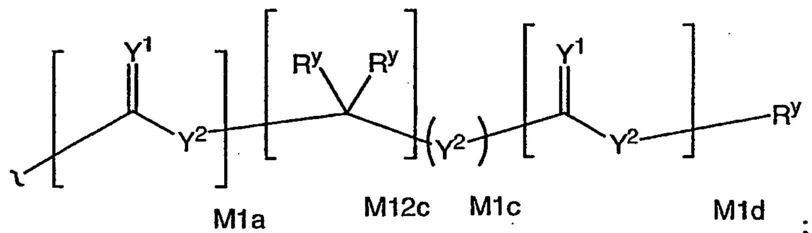
A^3 is:



Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)(R^x))$.

Y^2 is independently a bond, O, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)(R^x))$, $-S(O)_{M2}-$, or $-S(O)_{M2}-S(O)_{M2}-$.

R^x is independently H, W^3, a protecting group, or the formula:



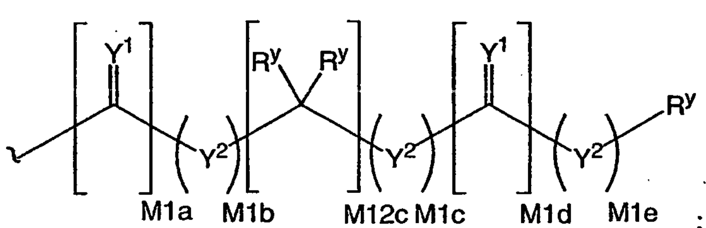
wherein:

M1a, M1c, and M1d are independently 0 or 1;

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12; and

R^y is independently H, W^3, R^2 or a protecting group.

Alternatively, R^x is a group of the formula:



wherein:

m1a, m1b, m1c, m1d and m1e are independently 0 or 1;

m12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

R^y is H, W^3, R^2 or a protecting group;

provided that:

if m1a, m12c, and m1d are 0, then m1b, m1c and m1e are 0;

if m1a and m12c are 0 and m1d is not 0, then m1b and m1c are 0;

if m1a and m1d are 0 and m12c is not 0, then m1b and at least one of m1c and m1e are 0;

if m1a is 0 and m12c and m1d are not 0, then m1b is 0;

if m12c and m1d are 0 and m1a is not 0, then at least two of m1b, m1c and m1e are 0;

if m12c is 0 and m1a and m1d are not 0, then at least one of m1b and m1c are 0; and

if m1d is 0 and m1a and m12c are not 0, then at least one of m1c and m1e are 0.

R^1 is independently H or alkyl of 1 to 18 carbon atoms.

R^2 is independently H, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups. Alternatively, taken together at a carbon atom, two R^2 groups form a ring, i.e. a spiro carbon. The ring may be, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. The ring may be substituted with 0 to 3 R^3 groups.

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d}.

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$.

R^{3b} is Y^1.

R^{3c} is $-R^x$, $-N(R^x)(R^x)$, $-SR^x$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^x)$, $-S(O)_2(OR^x)$, $-OC(Y^1)R^x$, $-OC(Y^1)OR^x$, $-OC(Y^1)(N(R^x)(R^x))$, $-SC(Y^1)R^x$, $-SC(Y^1)OR^x$, $-SC(Y^1)(N(R^x)(R^x))$, $-N(R^x)C(Y^1)R^x$, $-N(R^x)C(Y^1)OR^x$, or $-N(R^x)C(Y^1)(N(R^x)(R^x))$.

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)(N(R^x)(R^x))$.

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms.

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups.

R^{5a} is independently alkylene of 1 to 18 carbon atoms, alkenylene of 2 to 18 carbon atoms, or alkynylene of 2-18 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R^3 groups.

W^3 is W^4 or W^5.

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_2R^5$, or $-SO_2W^5$.

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups.

W^{3a} is W^{4a} or W^{5a}.

W^{4a} is R^{5a}, $-C(Y^1)R^{5a}$, $-C(Y^1)W^{5a}$, $-SO_2R^{5a}$, or $-SO_2W^{5a}$.

W^{5a} is a multivalent substituted carbocycle or heterocycle wherein W^{5a} is independently substituted with 0 to 3 R^2 groups.

W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups.

M2 is 0, 1 or 2;

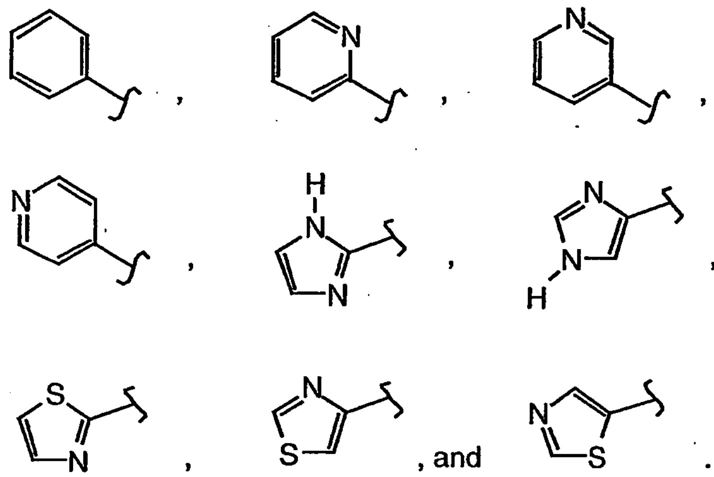
M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12; and

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

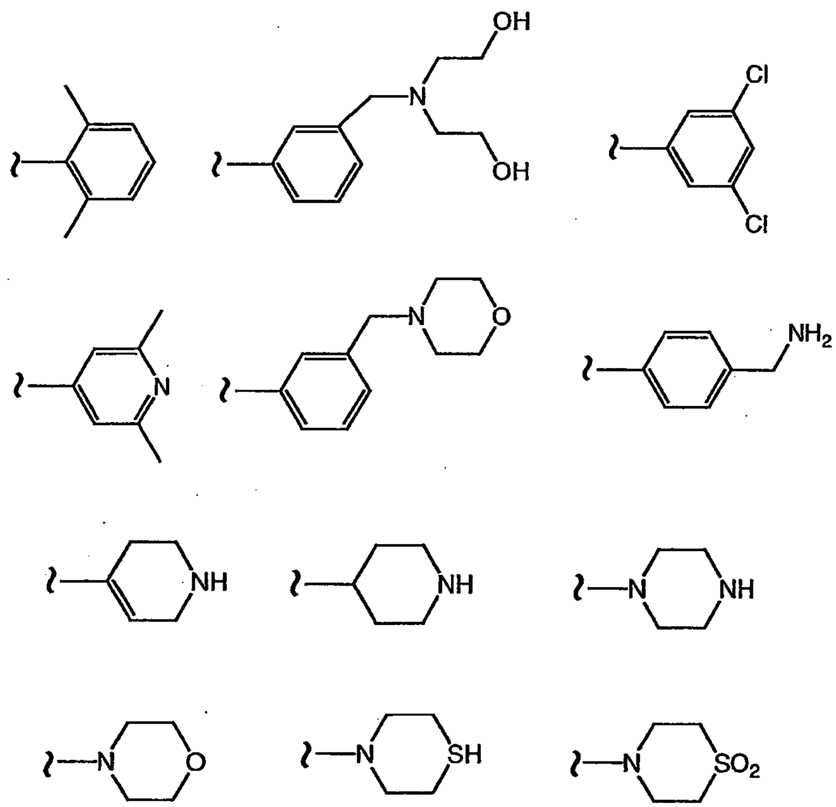
W^5 and W^{5a} carbocycles and W^5 and W^{5a} heterocycles may be independently substituted with 0 to 3 R^2 groups. W^5 may be a saturated, unsaturated or aromatic ring comprising a mono- or bicyclic carbocycle or heterocycle. W^5 may have 3 to 10 ring atoms, e.g., 3 to 7 ring atoms. The W^5 rings are saturated when containing 3 ring atoms, saturated or mono-unsaturated when containing 4 ring atoms, saturated, or mono- or di-unsaturated when containing 5 ring atoms, and saturated, mono- or di-unsaturated, or aromatic when containing 6 ring atoms.

A W^5 or W^{5a} heterocycle may be a monocycle having 3 to 7 ring members (2 to 6 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S) or a bicycle having 7 to 10 ring members (4 to 9 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S). W^5 and W^{5a} heterocyclic monocycles may have 3 to 6 ring atoms (2 to 5 carbon atoms and 1 to 2 heteroatoms selected from N, O, and S); or 5 or 6 ring atoms (3 to 5 carbon atoms and 1 to 2 heteroatoms selected from N and S). W^5 and W^{5a} heterocyclic bicycles have 7 to 10 ring atoms (6 to 9 carbon atoms and 1 to 2 heteroatoms selected from N, O, and S) arranged as a bicyclo [4,5], [5,5], [5,6], or [6,6] system; or 9 to 10 ring atoms (8 to 9 carbon atoms and 1 to 2 hetero atoms selected from N and S) arranged as a bicyclo [5,6] or [6,6] system. The W^5 heterocycle may be bonded to Y^2 through a carbon, nitrogen, sulfur or other atom by a stable covalent bond.

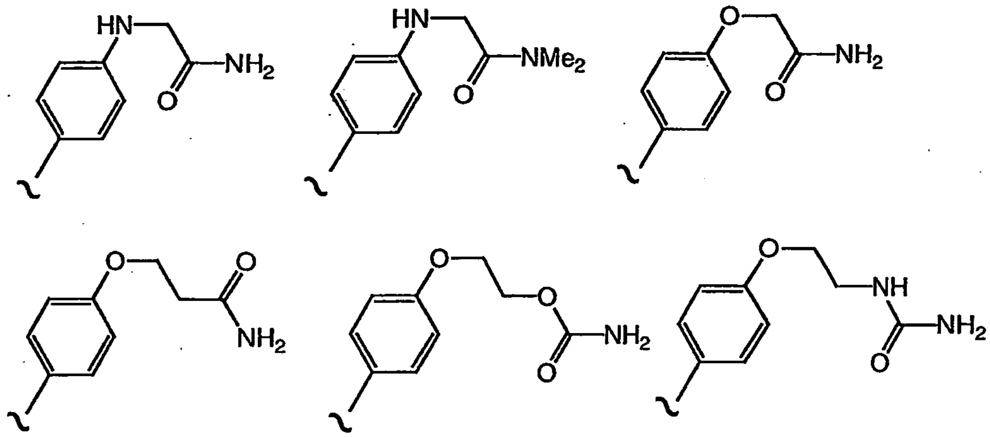
W^5 and W^{5a} heterocycles include for example, pyridyl, dihydropyridyl isomers, piperidine, pyridazinyl, pyrimidinyl, pyrazinyl, s-triazinyl, oxazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, furanyl, thiofuranyl, thienyl, and pyrrolyl. W^5 also includes, but is not limited to, examples such as:



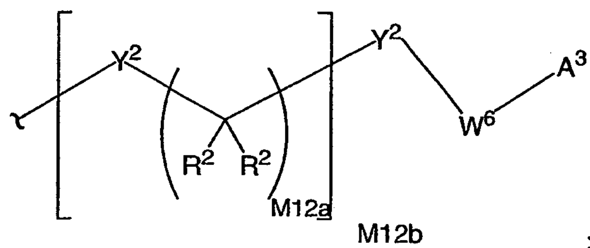
W^5 and W^{5a} carbocycles and heterocycles may be independently substituted with 0 to 3 R^2 groups, as defined above. For example, substituted W^5 carbocycles include:



Examples of substituted phenyl carbocycles include:

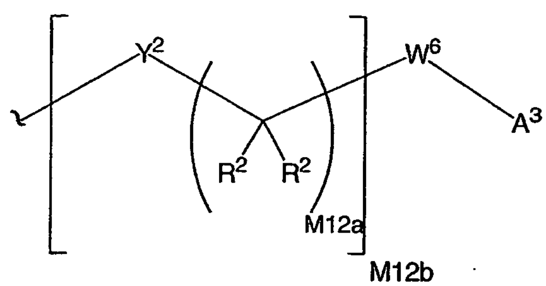


Embodiments of A^1 include:

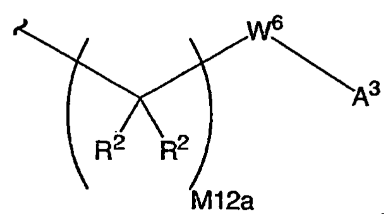


;

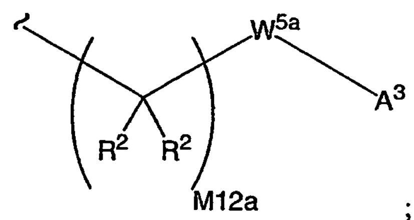
and where one or more Y^2 are a bond, such as:



,



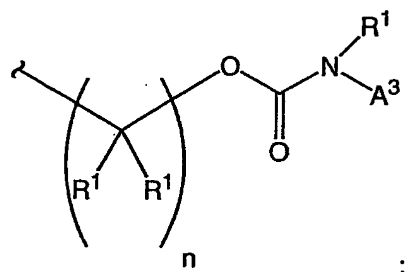
, and



;

where W^{5a} is a carbocycle or a heterocycle and W^{5a} is independently substituted with 0 or 1 R^2 groups.

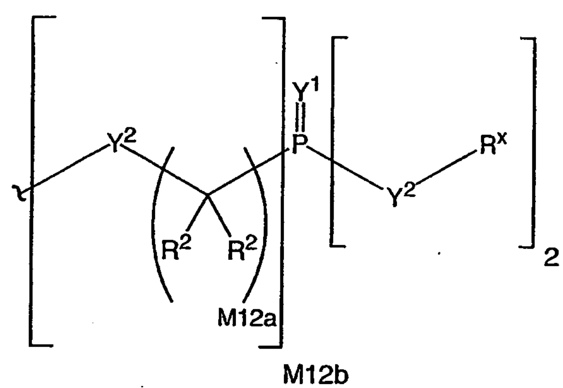
Embodiments of A^1 also include:



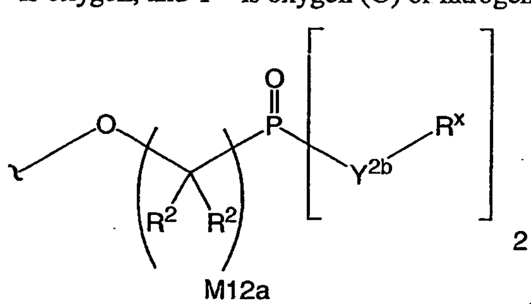
;

where n is an integer from 1 to 18.

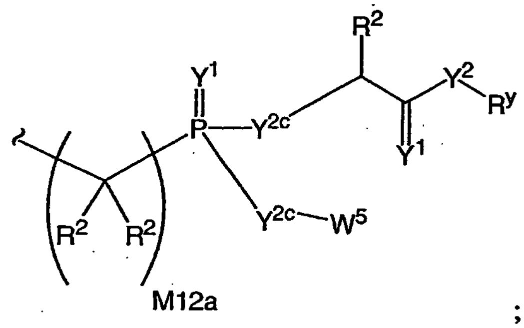
Embodiments of A^3 include where M2 is 0, such as:



and where M12b is 1, Y^1 is oxygen, and Y^{2b} is oxygen (O) or nitrogen ($N(R^x)$) such as:

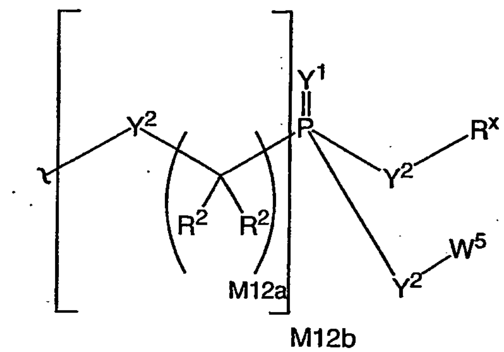


An embodiment of A^3 includes:

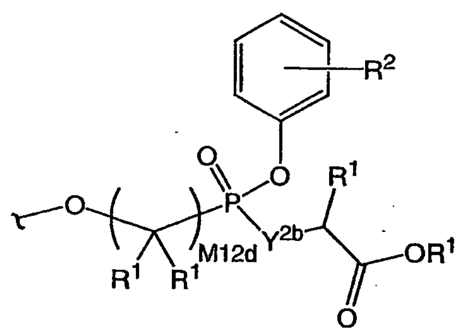


where Y^{2c} is O, $N(R^y)$ or S. For example, R^1 may be H and n may be 1.

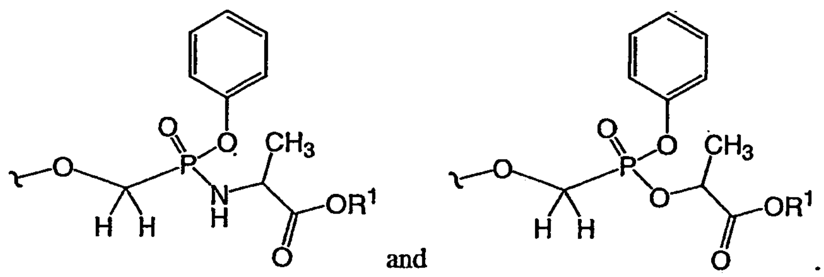
Another embodiment of A^3 includes:



where W^5 is a carbocycle such as phenyl or substituted phenyl. Such embodiments include:

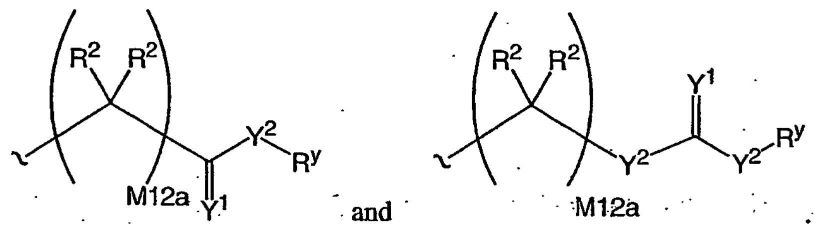


where Y^{2b} is O or $N(R^x)$; M12d is 1, 2, 3, 4, 5, 6, 7 or 8; and the phenyl carbocycle is substituted with 0 to 3 R^2 groups. Such embodiments of A^3 include phenyl phosphonamidate amino acid, e.g. alanate esters and phenyl phosphonate-lactate esters:

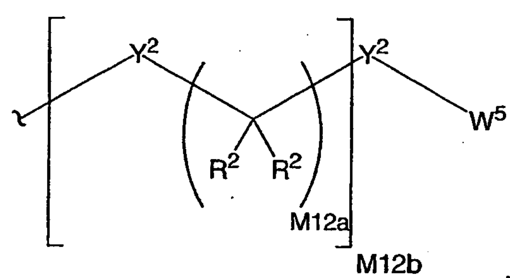


The chiral carbon of the amino acid and lactate moieties may be either the R or S configuration or the racemic mixture.

Embodiments of R^x include esters, carbamates, carbonates, thioesters, amides, thioamides, and urea groups:

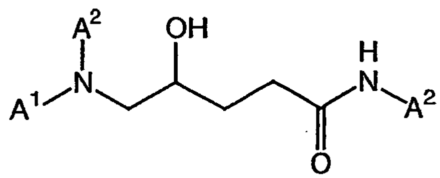


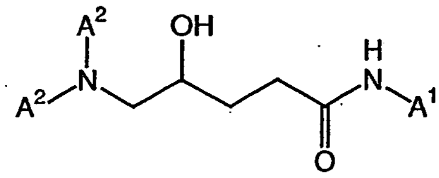
Embodiments of A^2 include where W^3 is W^5, such as:

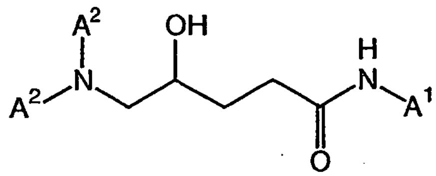


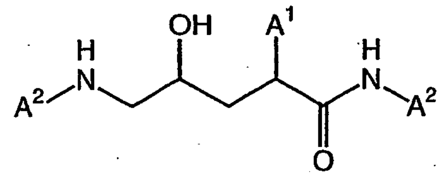
Alternatively, A^2 is phenyl, substituted phenyl, benzyl, substituted benzyl, pyridyl or substituted pyridyl.

Exemplary embodiments of Formula I compounds include, but are not limited to, structures:



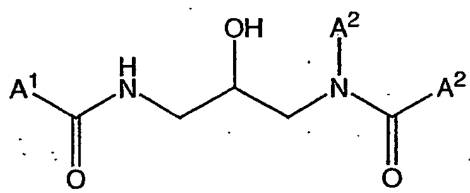


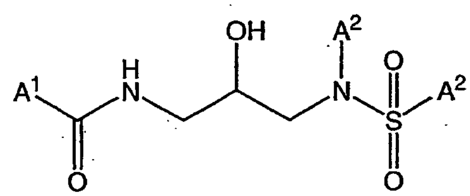


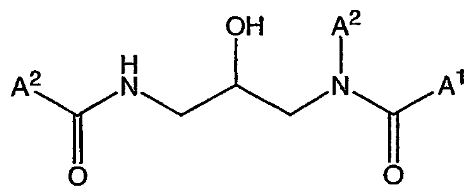


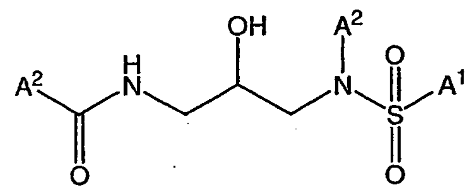
where A^1 denotes a covalent attachment site of a phosphonate group.

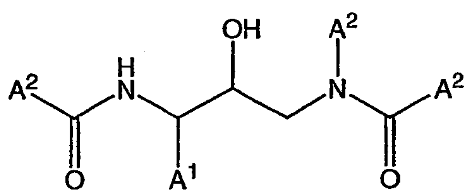
Exemplary embodiments of Formula II compounds include, but are not limited to, structures:

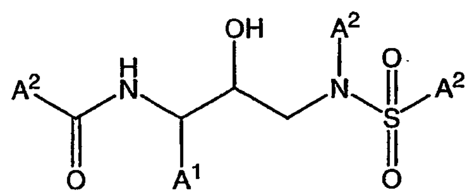






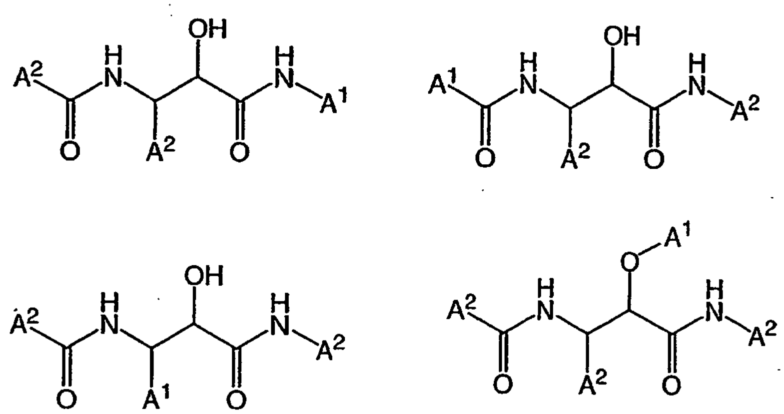






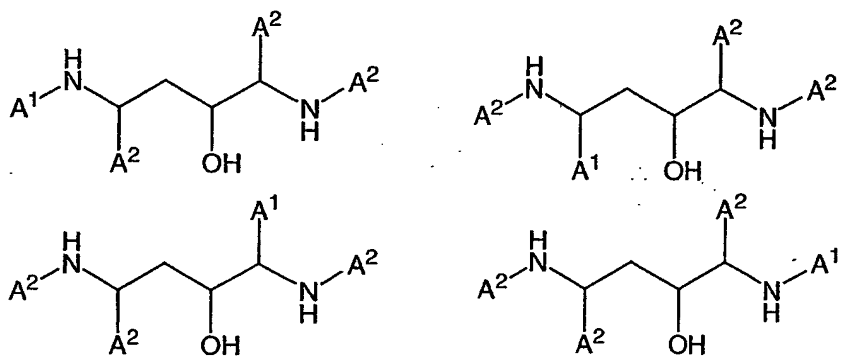
where A^1 denotes a covalent attachment site of a phosphonate group.

Exemplary embodiments of Formula III compounds include, but are not limited to, structures:

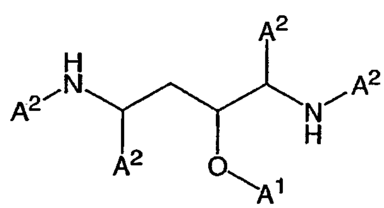


where A^1 denotes a covalent attachment site of a phosphonate group.

Exemplary embodiments of Formula IV compounds include, but are not limited to, structures:

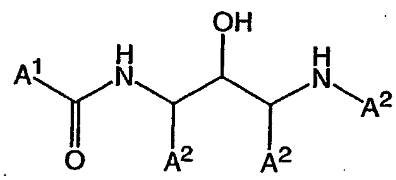


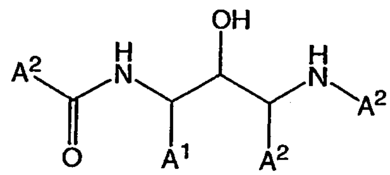
and

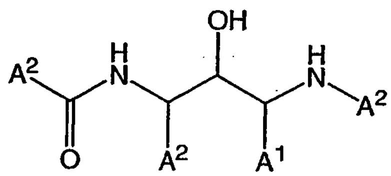


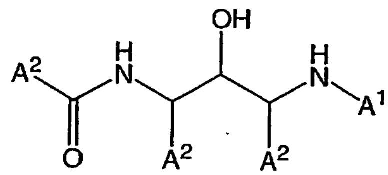
where A^1 denotes a covalent attachment site of a phosphonate group.

Exemplary embodiments of Formula V compounds include, but are not limited to, structures:

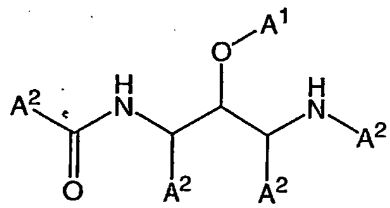






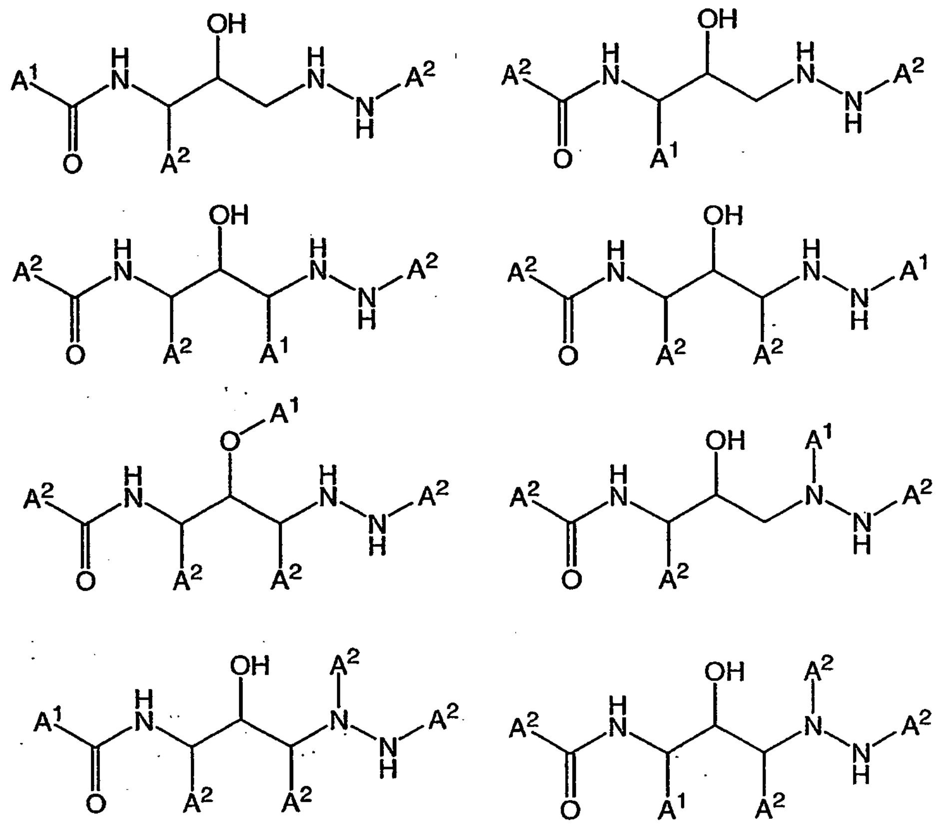


and



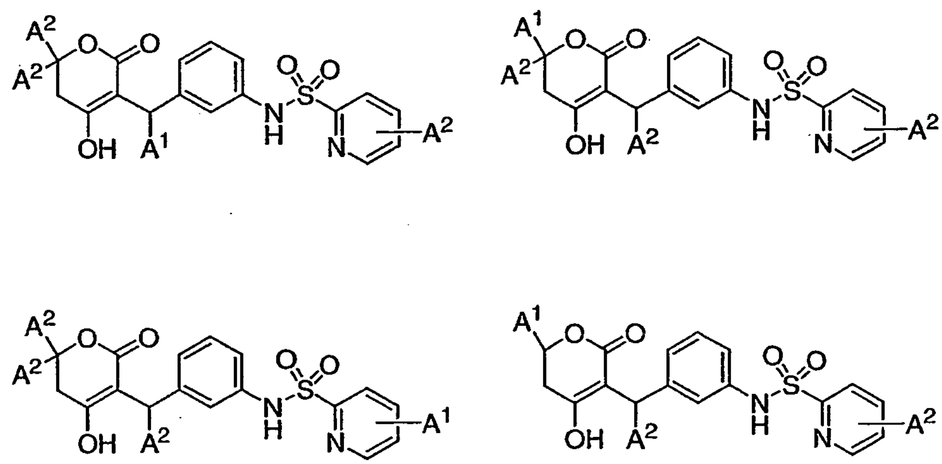
where A^1 denotes a covalent attachment site of a phosphonate group.

Exemplary embodiments of Formula VI compounds include, but are not limited to, structures:



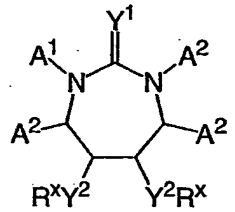
where A^1 denotes a covalent attachment site of a phosphonate group.

Exemplary embodiments of Formula VII compounds include, but are not limited to, structures:

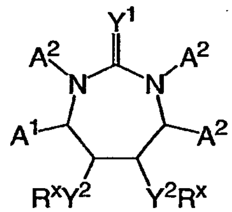


where A^1 denotes a covalent attachment site of a phosphonate group.

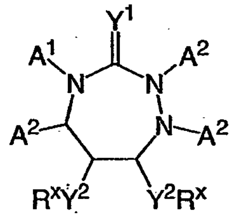
Exemplary embodiments of Formula VIIIa compounds include structures:

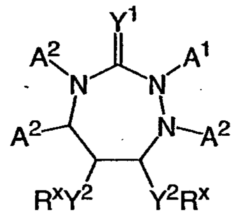


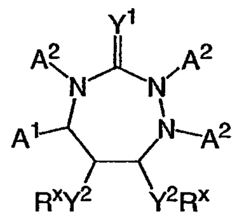
and



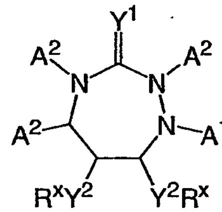
Exemplary embodiments of Formula VIIIb compounds include structures:







and



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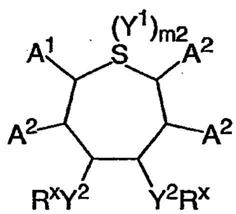
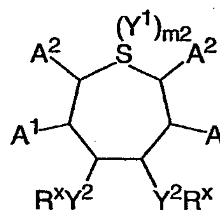
Exemplary embodiments of Formula VIIIc compounds include structures:



and



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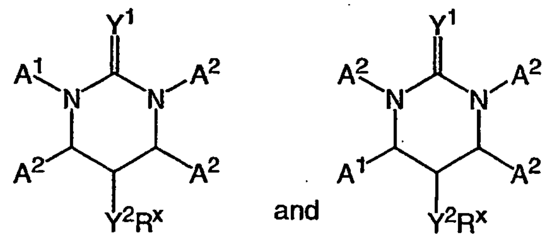
Exemplary embodiments of Formula VIIId compounds include structures:



where A^1 denotes a covalent attachment site of a phosphonate group.

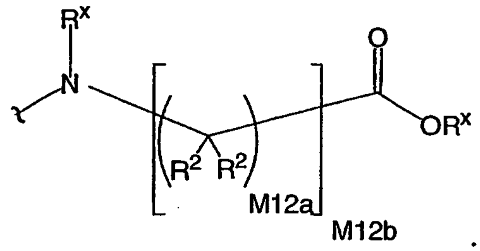
A Cellular Accumulation Embodiment

Another embodiment of the invention is directed toward an HIV protease inhibitor compound capable of accumulating in human PBMCs. Accumulation in human PBMCs is described in the examples herein. Typically, the compounds of this embodiment further comprise a phosponate or phosphonate prodrug. More typically, the phosphonate or phosphonate prodrug has the structure A^3 as described herein. Each of the preferred embodiments of A^3 described herein is a preferred embodiment of A^3 in the present embodiment.

Optionally, the compounds of this embodiment demonstrate improved intracellular half-life of the compounds or intracellular metabolites of the compounds in human PBMCs when compared to analogs of the compounds not having the phosphonate or phosphonate prodrug. Typically, the half-life is improved by at least about 50%, more typically at least in the range 50-100%, still more typically at least about 100%, more typically yet greater than about 100%.

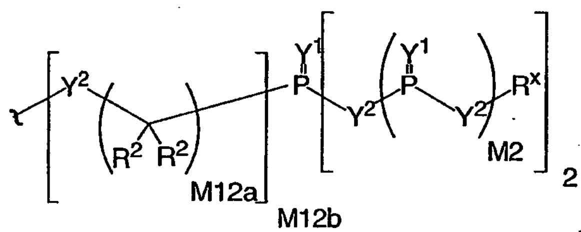
In a preferred embodiment, the intracellular half-life of a metabolite of the compound in human PBMCs is improved when compared to an analog of the compound not having the phosphonate or phosphonate prodrug. In such embodiments, the metabolite is typically generated intracellularly, more typically, it is generated within human PBMCs. Still more typically, the metabolite is a product of the cleavage of a phosphonate prodrug within human PBMCs. More typically yet, the phosphonate prodrug is cleaved to form a metabolite having at least one negative charge at physiological pH. Most typically, the phosphonate prodrug is enzymatically cleaved within human PBMCs to form a phosphonate having at least one active hydrogen atom of the form P-OH.

Not withstanding other disclosure herein which describes the role or presents of phosphonates in the compounds of the invention, in another embodiment of the invention A^3 is A^{3a} which is of the formula:



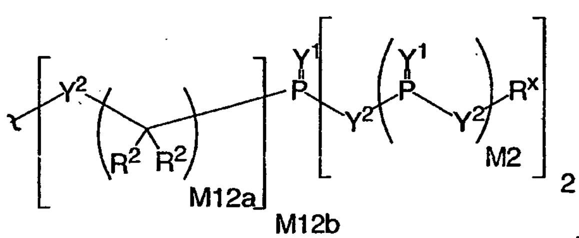
In this embodiment of the invention, any A^3 group may be A^{3a}.

In another aspect of the invention, A^3 is of the formula:



M12a is other than 0 and at least one phosphonate group present in the compound is not bonded directly to W^3. More typically, the phosphonate is not bonded directly to W^5. In such an embodiment, the phosphorous atom of the phosphonate is not bonded directly to a carbon atom of a ring.

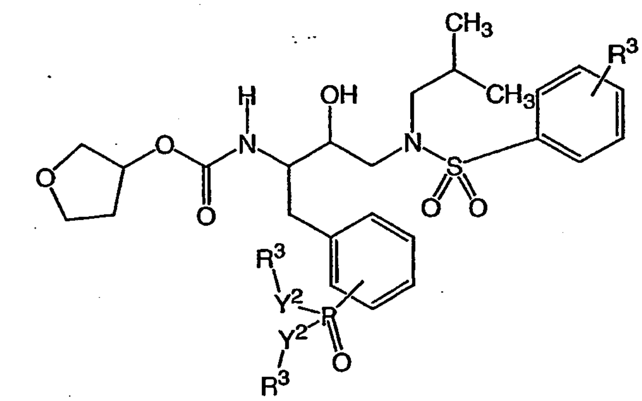
In another aspect of the invention an Amprenavir like phosphonate protease inhibitor, as described above in the description and below in the claims, contains an A^3 group of the formula:



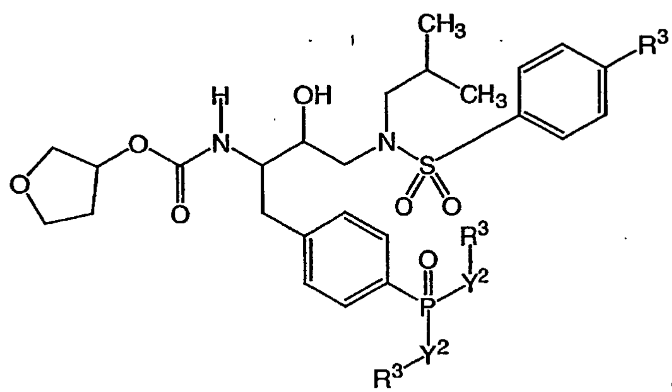
M12a is other than 0 and at least one phosphonate group present in the compound is not bonded directly to W^3. More typically, the phosphonate is not bonded directly to W^5. In

such an embodiment, the phosphorous atom of the phosphonate is not bonded directly to a carbon atom of a ring.

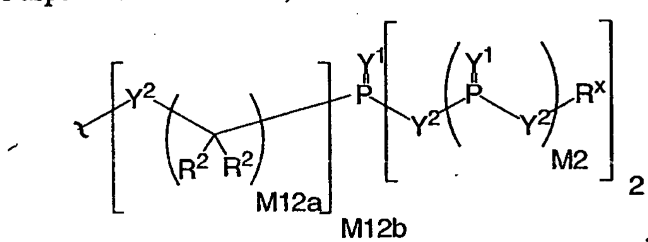
One embodiment of Amprenavir like phosphonate protease inhibitors as described above in the description and below in the claims excludes compounds of the formulas:



or

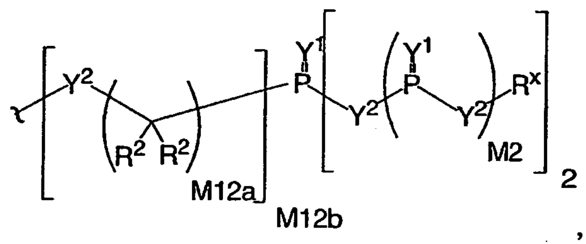


In another aspect of the invention, A^3 is of the formula:



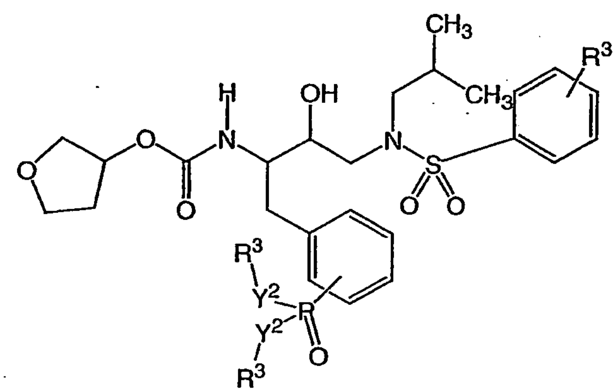
M12a is 0 and at least one phosphonate group present in the compound is bonded directly to W^3. More typically, the phosphonate is bonded directly to W^5. In such an embodiment, the phosphorous atom of the phosphonate is bonded directly to a carbon atom of a ring.

In another aspect of the invention an Amprenavir like phosphonate protease inhibitor, as described above in the description and below in the claims, contains an A^3 group of the formula:

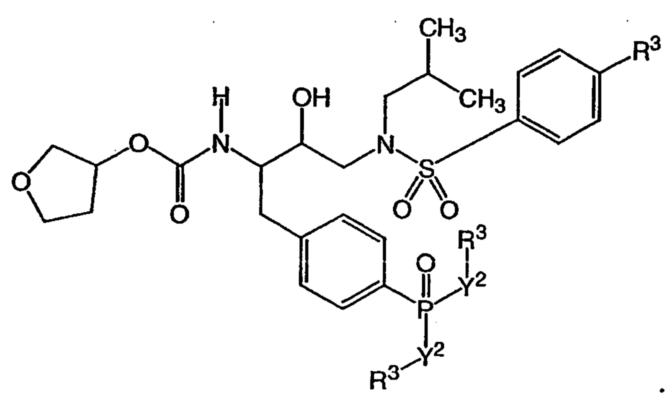


M12a is 0 and at least one phosphonate group present in the compound is bonded directly to W^3. More typically, the phosphonate is bonded directly to W^5. In such an embodiment, the phosphorous atom of the phosphonate is bonded directly to a carbon atom of a ring.

One embodiment of Amprenavir like phosphonate protease inhibitors as described above in the description and below in the claims is directed to compounds of the formulas:

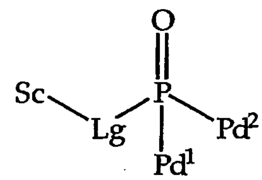


or



Exemplary Enumerated Compounds.

By way of example and not limitation, embodiments of the invention are named below in tabular format (Table 100). These embodiments are of the general formula "MBF":



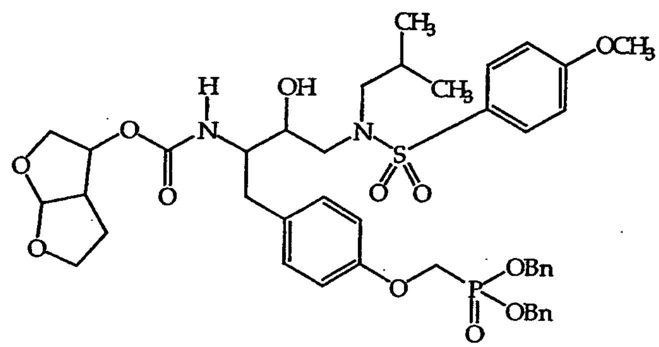
MBF

Each embodiment of MBF is depicted as a substituted nucleus (Sc) in which the nucleus is designated by a number and each substituent is designated in order by letter or number. Tables 1.1 to 1.5 are a schedule of nuclei used in forming the embodiments of Table 100. Each nucleus (Sc) is given a number designation from Tables 1.1 to 1.5, and this designation appears first in each embodiment name. Similarly, Tables 10.1 to 10.19 and 20.1 to 20.36 list the selected linking groups (Lg) and prodrug (Pd^1 and Pd^2) substituents, again by letter or number designation, respectively.

Accordingly, each named embodiment of Table 100 is depicted by a number designating the nucleus from Table 1.1-1.5, followed by a letter designating the linking group (Lg) from Table 10.1-10.19, and two numbers designating the two prodrug groups (Pd^1 and Pd^2) from Table 20.1-20.36. In graphical tabular form, each embodiment of Table 100 appears as a name having the syntax:

$$Sc.Lg.Pd^1.Pd^2$$

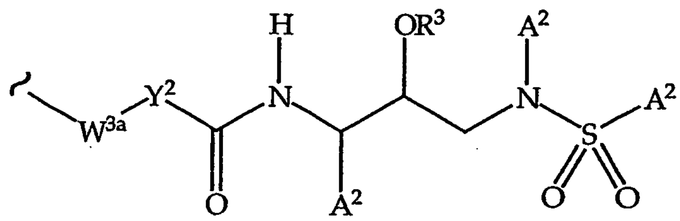
Thus, ignoring stereochemistry, structure 10, Scheme 2, Scheme Section A, is represented by 12.AH.247.247.



12.AH247.247

Each Sc group is shown having a tilda ("~"). The tilda is the point of covalent attachment of Sc to Lg. Q^1 and Q^2 of the linking groups (Lg), it should be understood, do not represent groups or atoms but are simply connectivity designations. Q^1 is the site of the covalent bond to the nucleus (Sc) and Q^2 is the site of the covalent bond to the phosphorous atom of formula MBF. Each prodrug group (Pd^1 and Pd^2) are covalently bonded to the phosphorous atom of MBF at the tilda symbol ("~"). Some embodiments of Tables 10.1-10.19 and 20.1-20.36 may be designated as a combination of letters and numbers (Table 10.1-10.19) or number and letter (Table 20.1-20.36). For example there are Table 10 entries for BJ1 and BJ2. In any event, entries of Table 10.1-10.19 always begin with a letter and those of Table 20.1-20.36 always begin with a number. When a nucleus (Sc) is shown enclosed within square brackets ("[]") and a covalent bond extends outside the brackets, the point of covalent attachment of Sc to Lg may be at any substitutable site on SC. Selection of the point of attachment is described herein. By way of example and not limitation, the point of attachment is selected from those depicted in the schemes and examples.

Table 1.1



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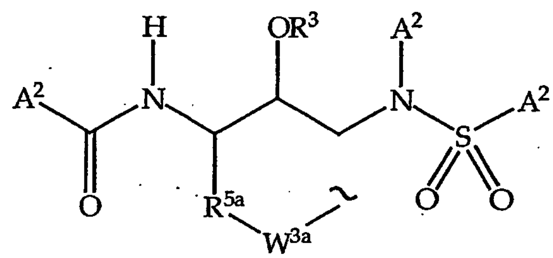

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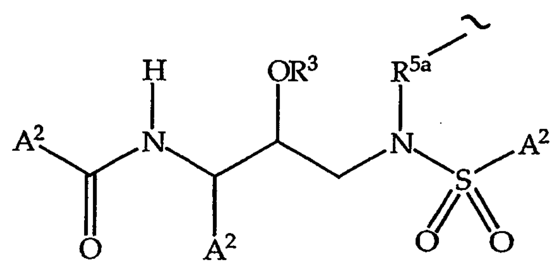

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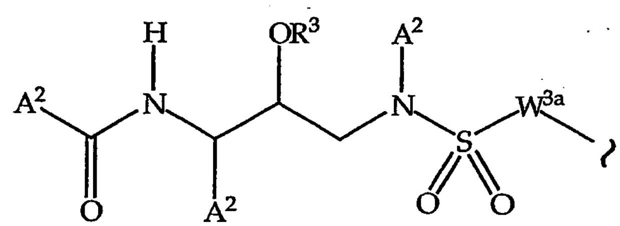

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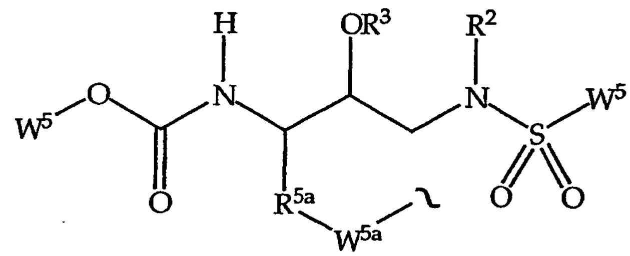
Table 1.2



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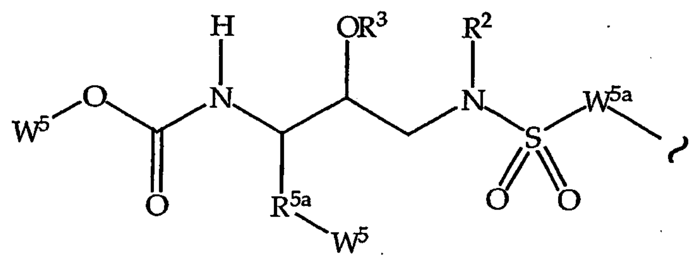
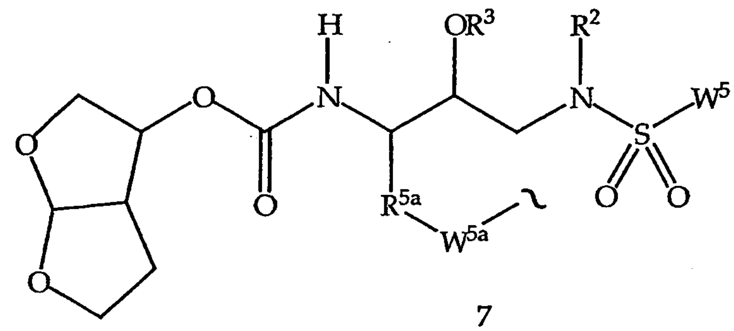


6

Table 1.3



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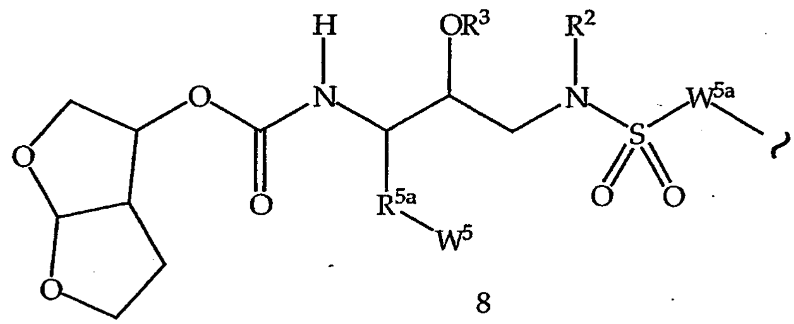

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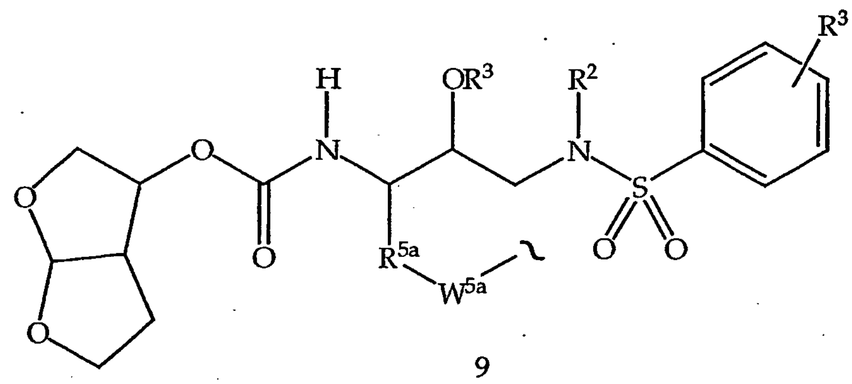

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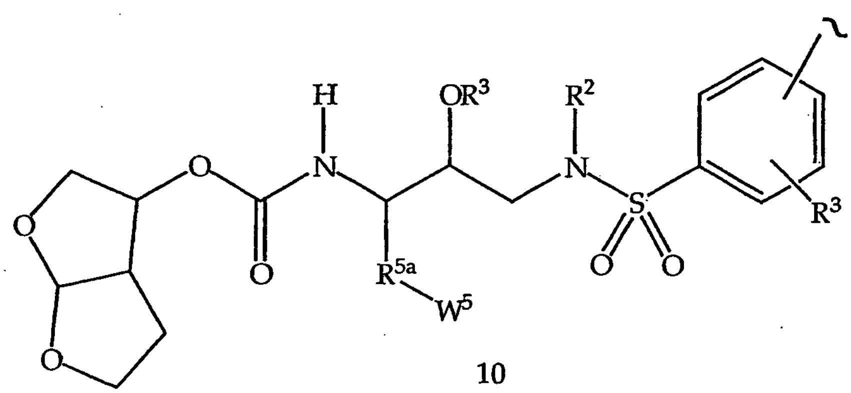

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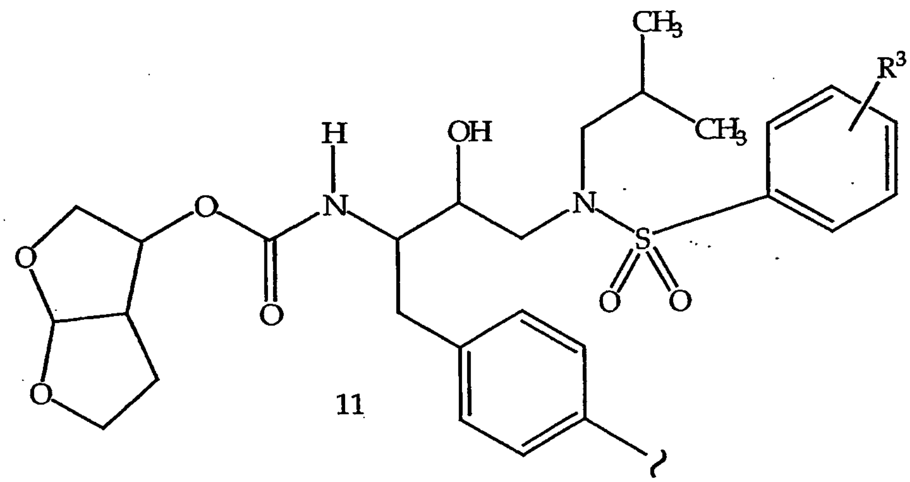
Table 1.4



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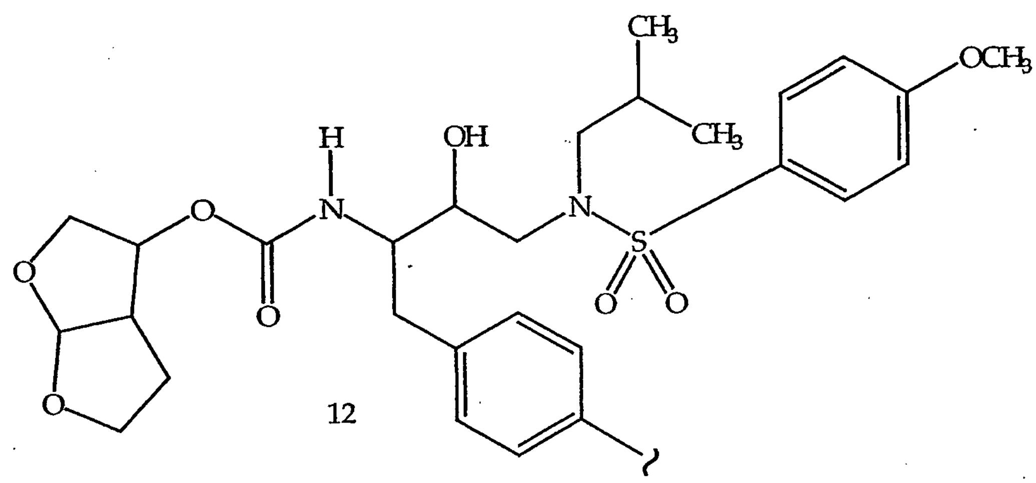

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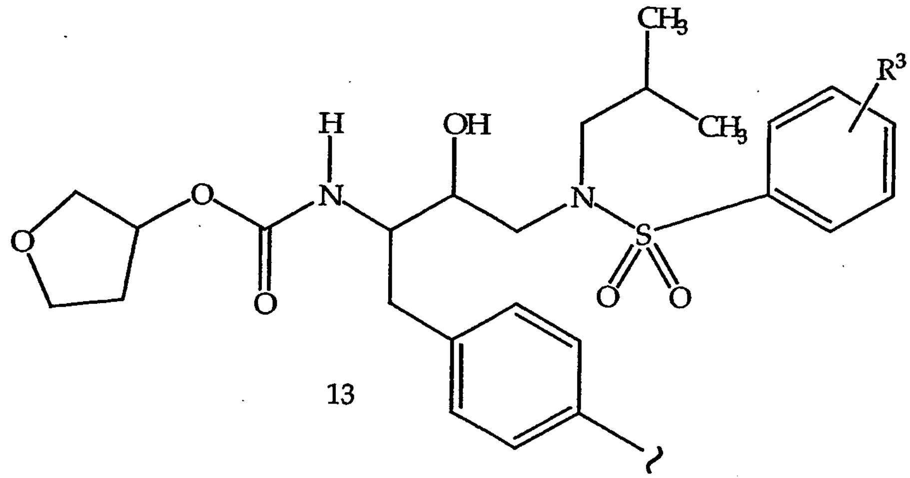
Table 1.5



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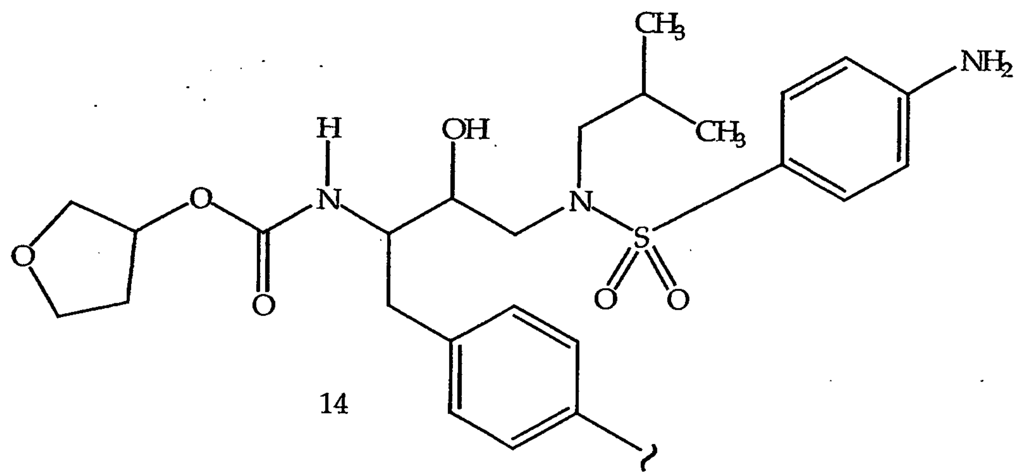

14

Table 10.1


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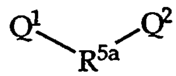
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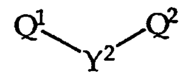
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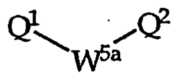
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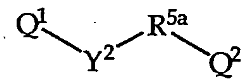
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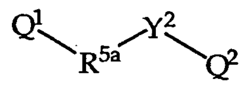
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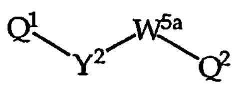
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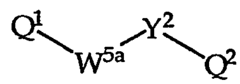
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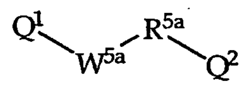
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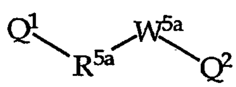
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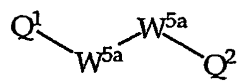
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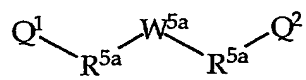
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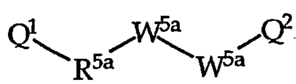
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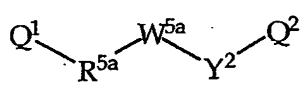
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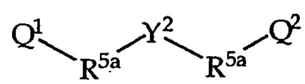
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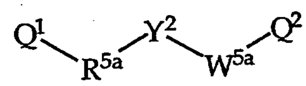

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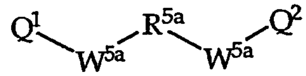

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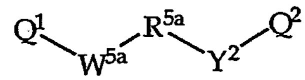

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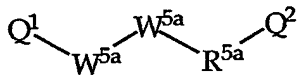

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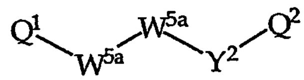

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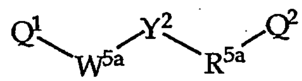

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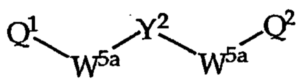

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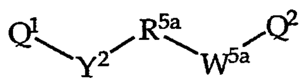

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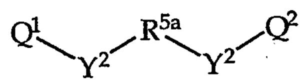

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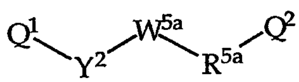

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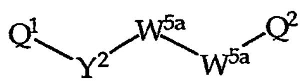

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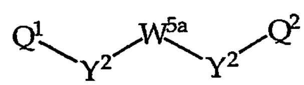

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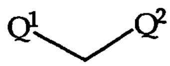

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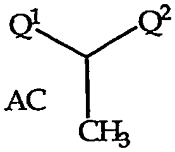

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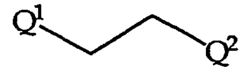

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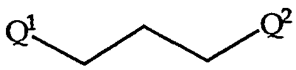

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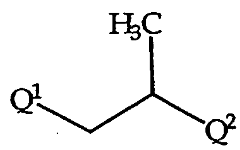

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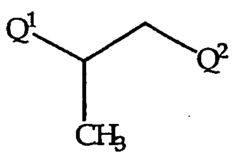

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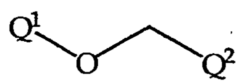

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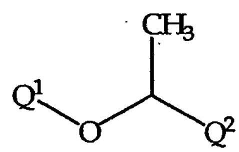

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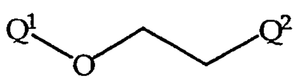

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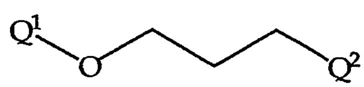

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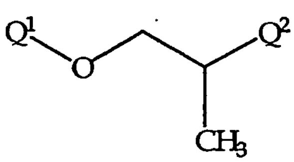

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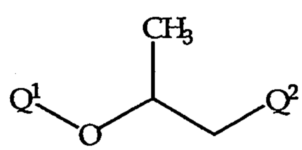

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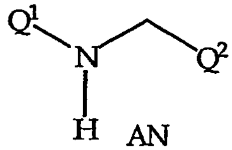
Table 10.4



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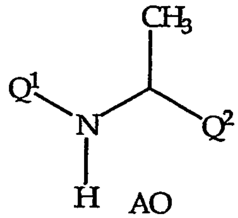

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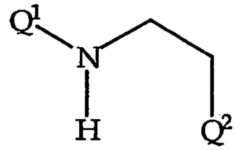

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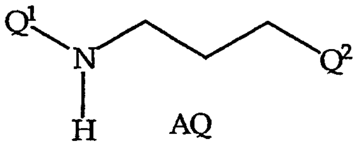

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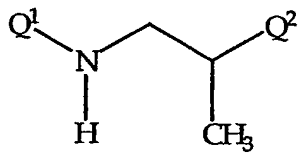

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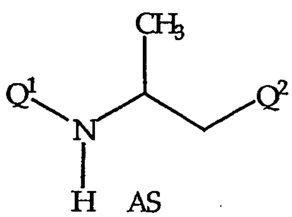

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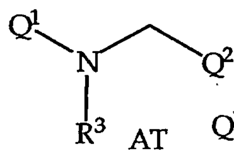

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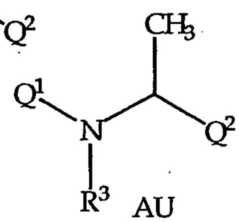

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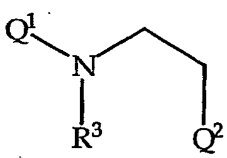

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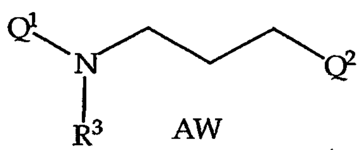

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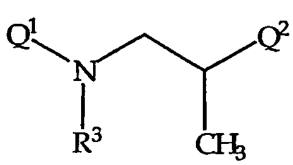

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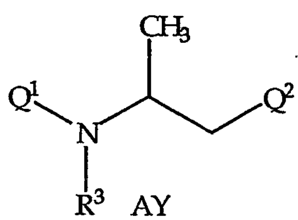

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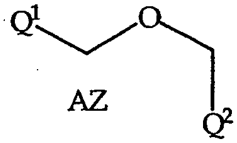
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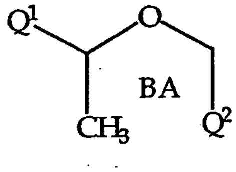
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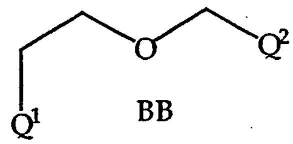
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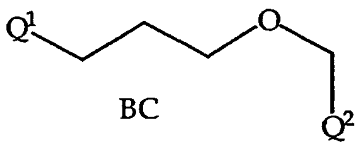
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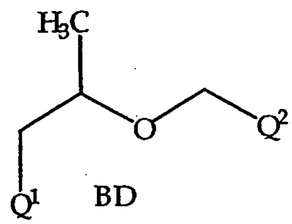
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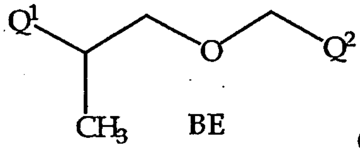
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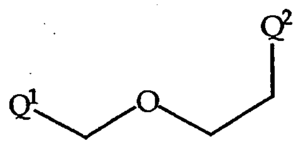
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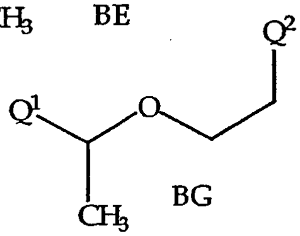
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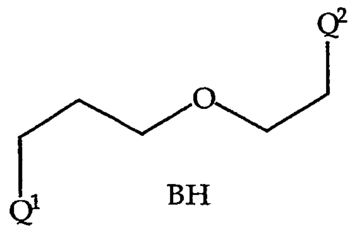
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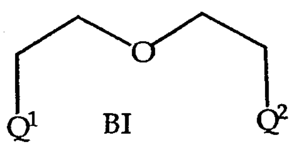
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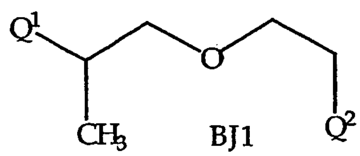
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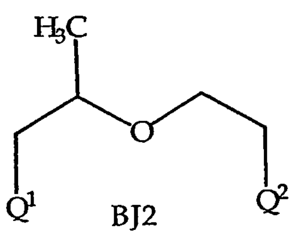
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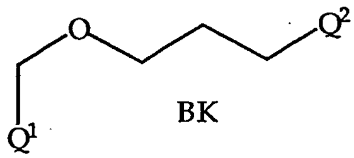

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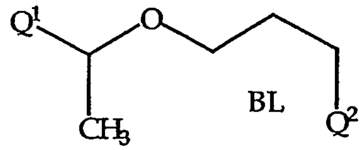

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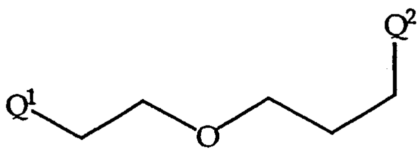

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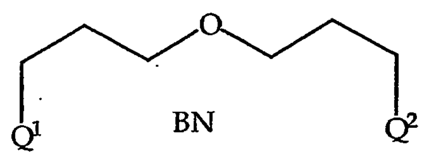

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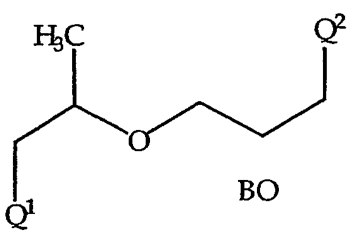

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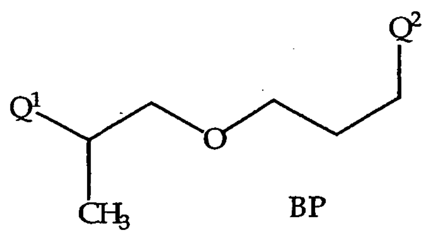

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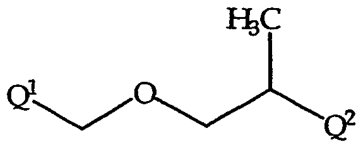

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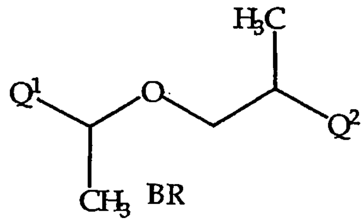

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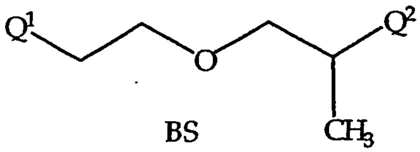

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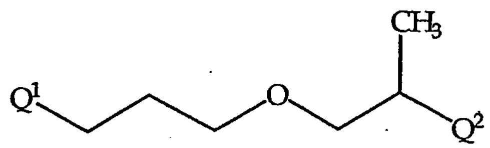

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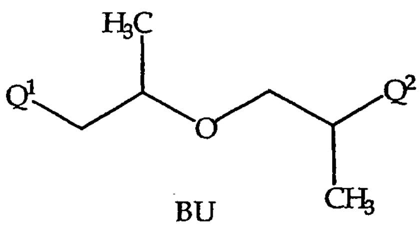

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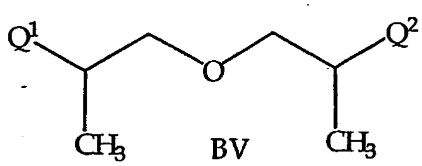

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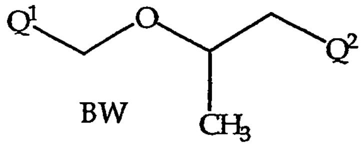

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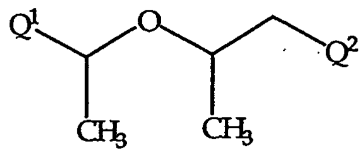

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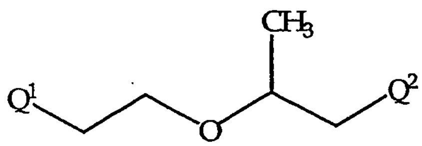

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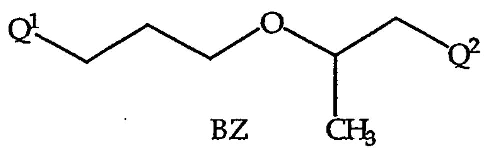

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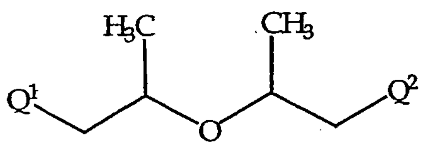

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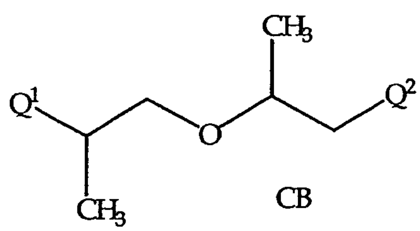

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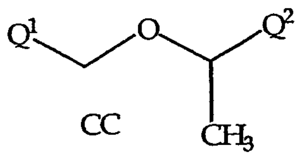

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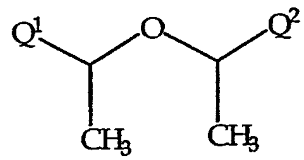

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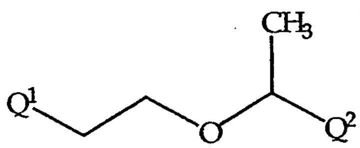

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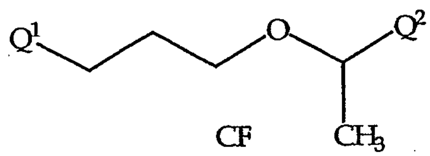

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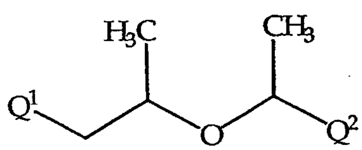

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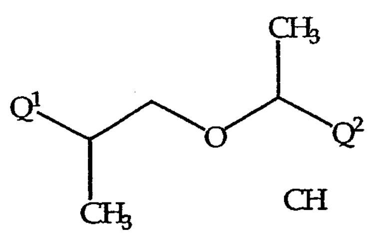

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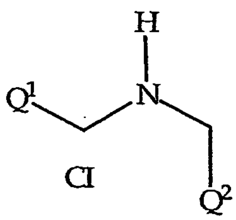
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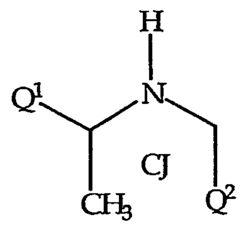
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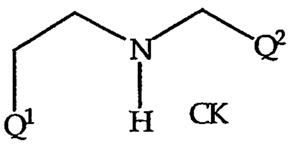
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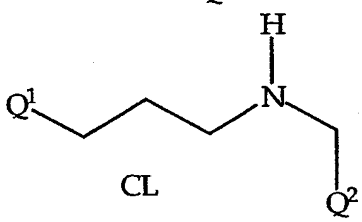
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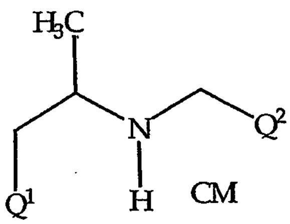
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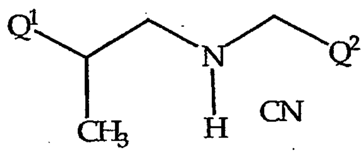
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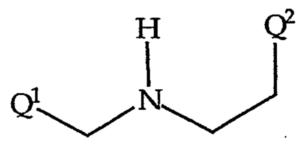
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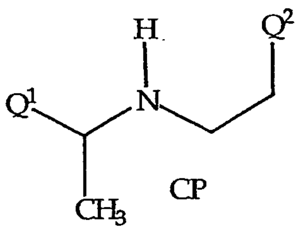
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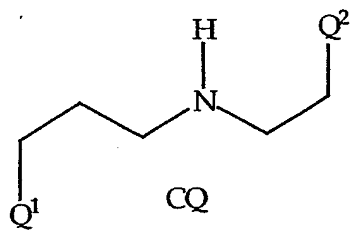
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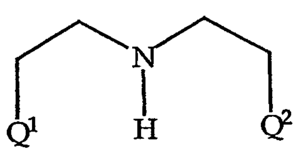
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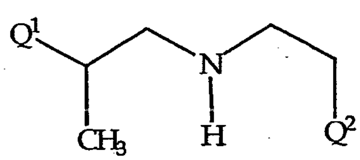
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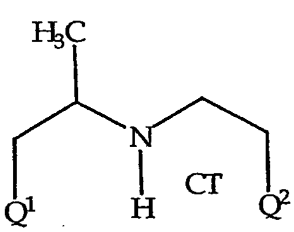
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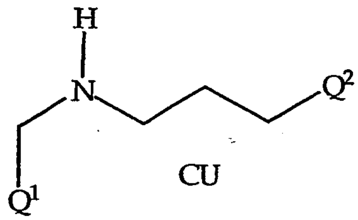

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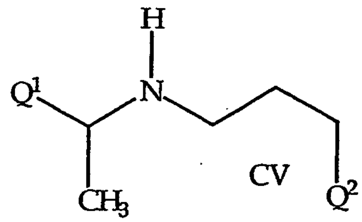

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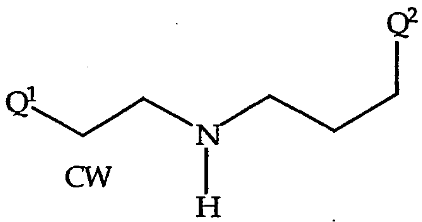

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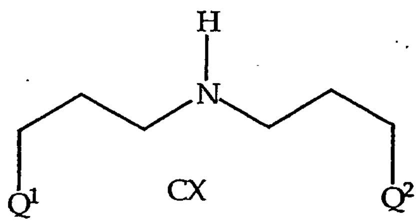

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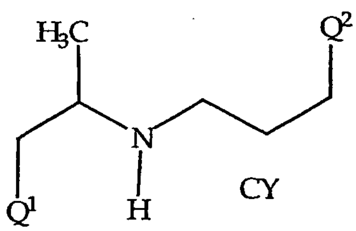

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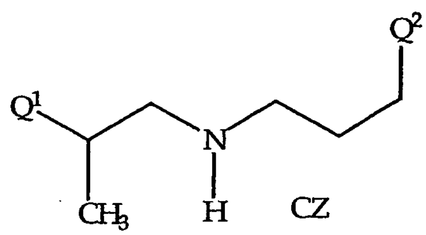

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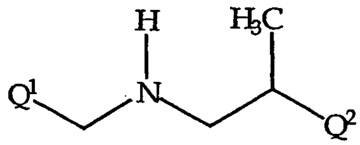

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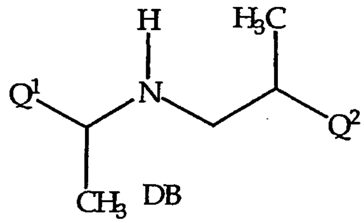

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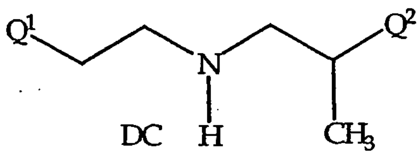

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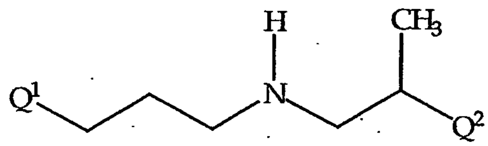

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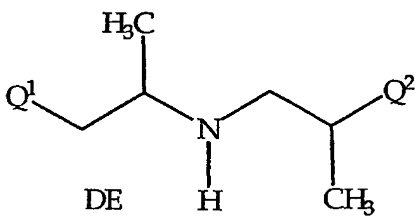

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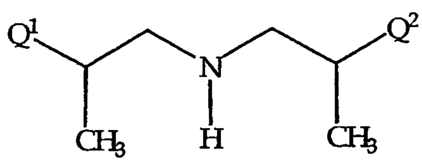

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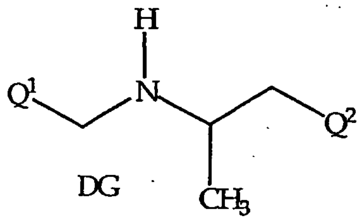

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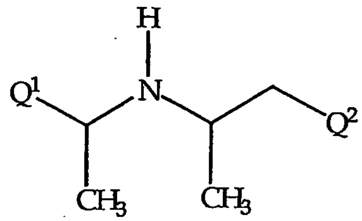

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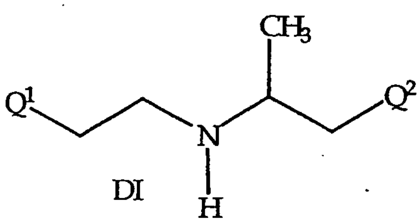

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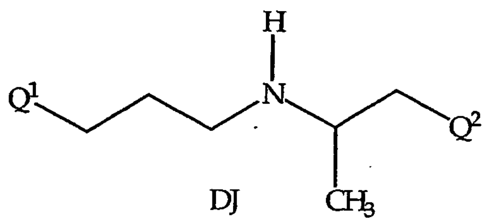

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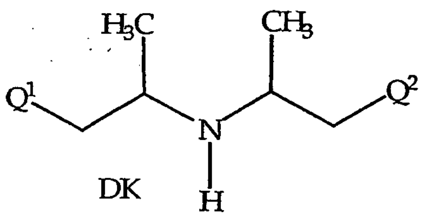

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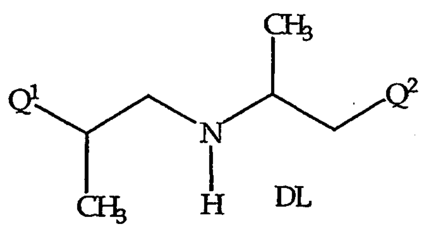

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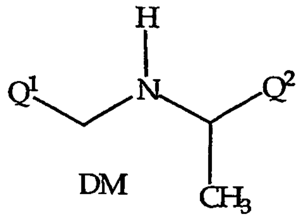

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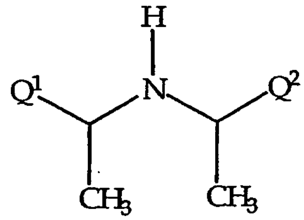

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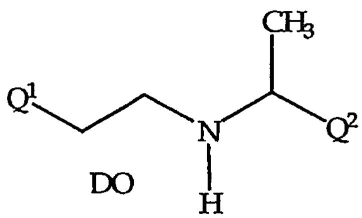

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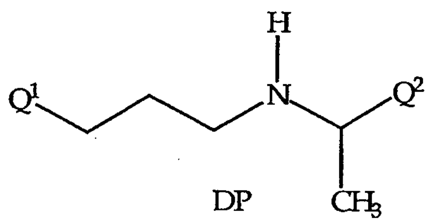

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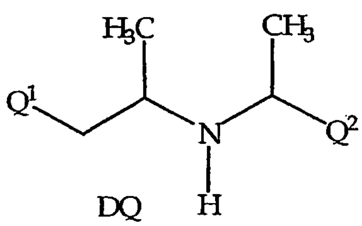

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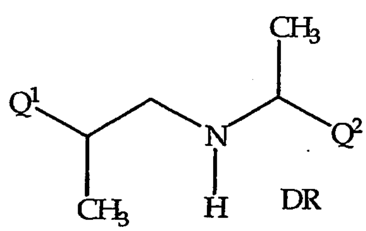

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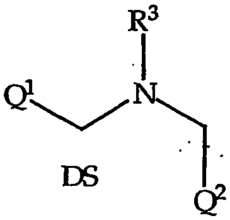
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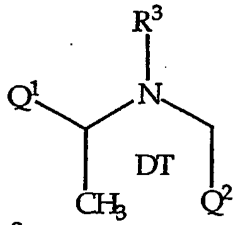
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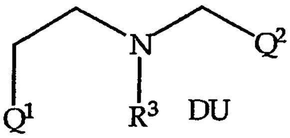
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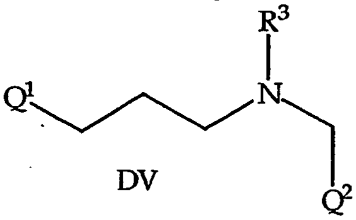
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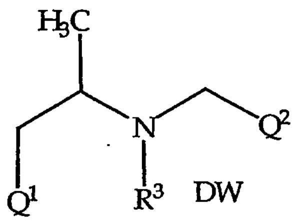
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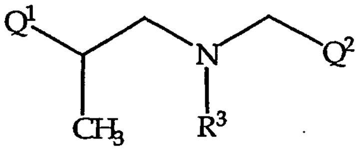
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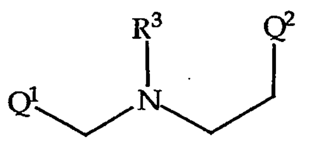
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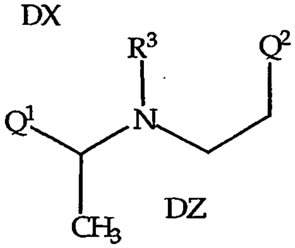
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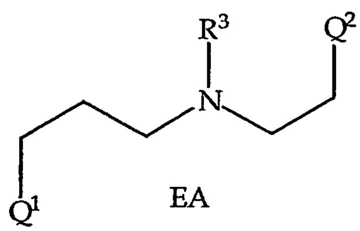
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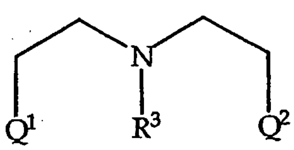
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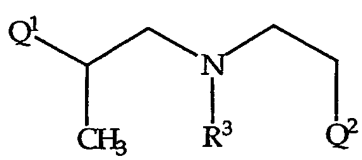
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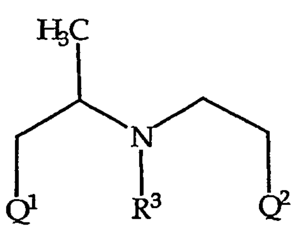
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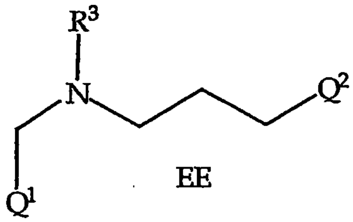

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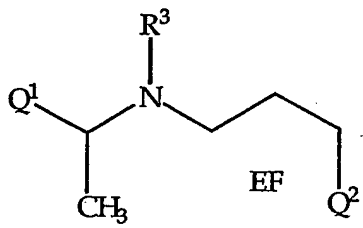

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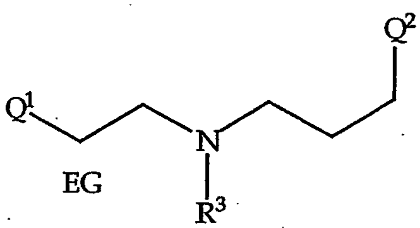

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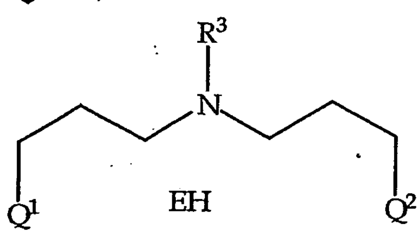

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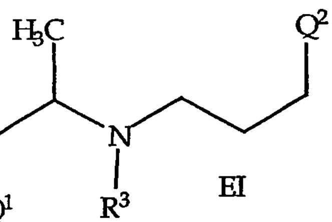

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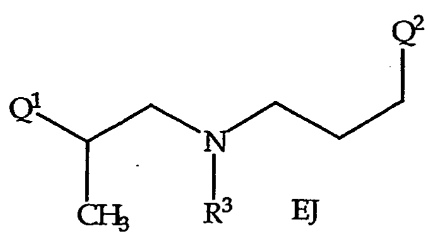

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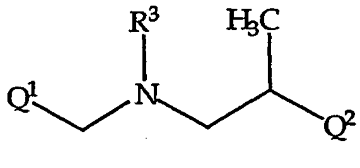

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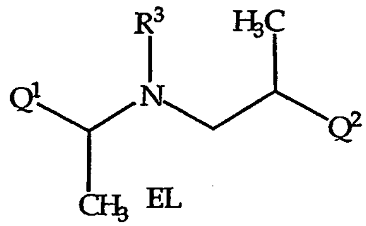

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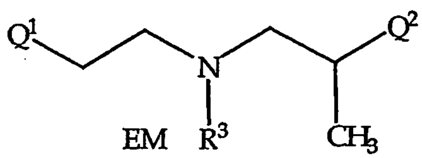

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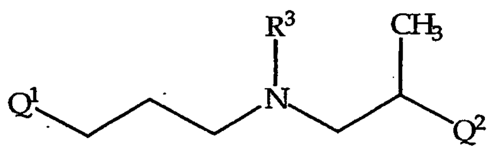

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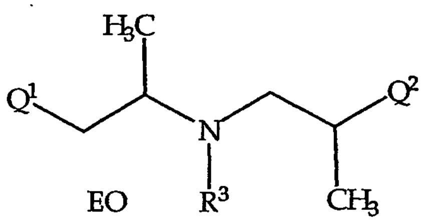

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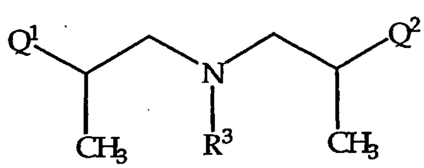

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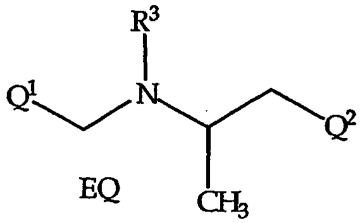

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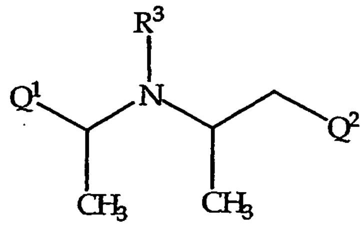

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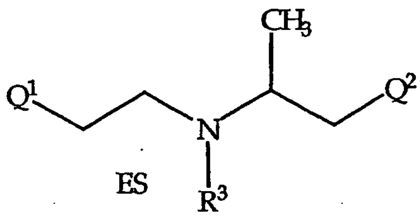

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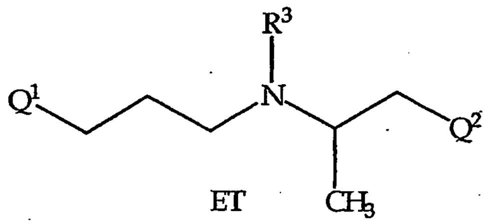

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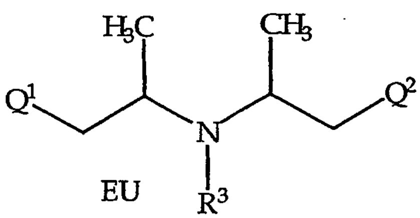

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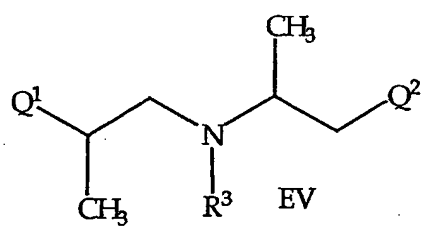

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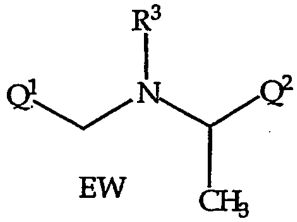

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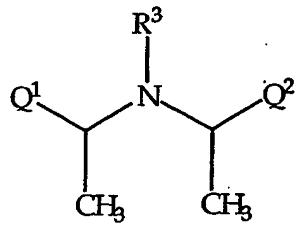

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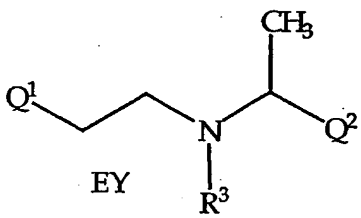

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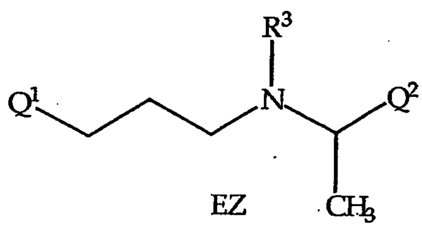

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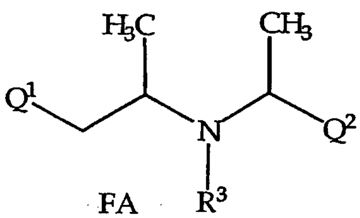

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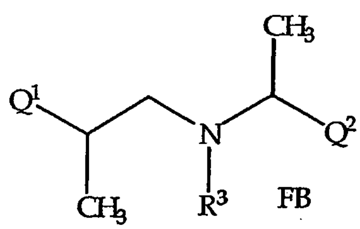

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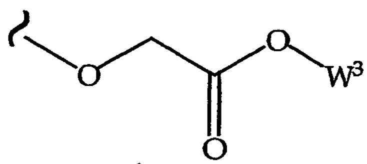
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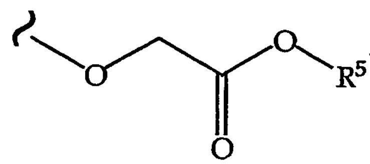
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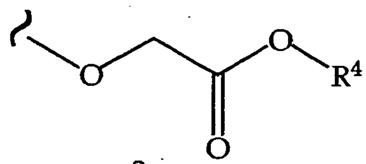
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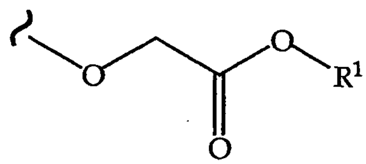
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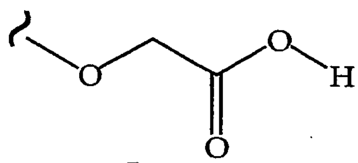
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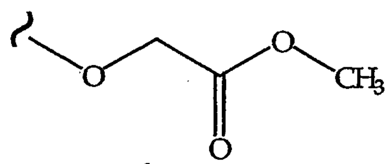
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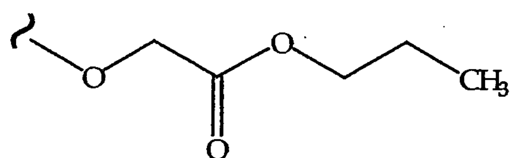
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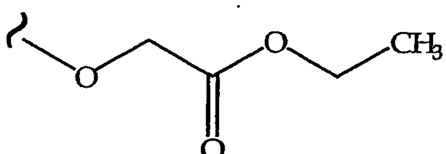
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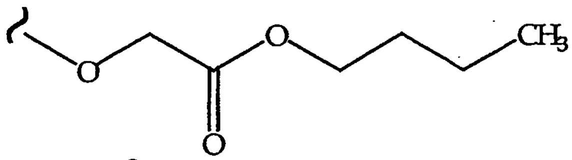

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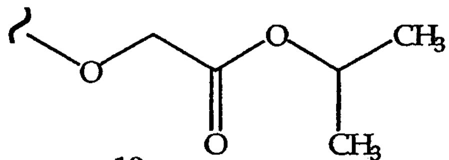

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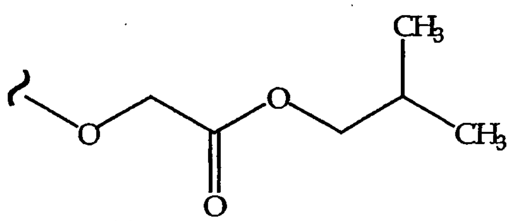

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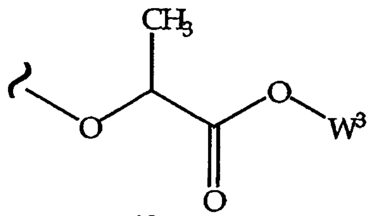

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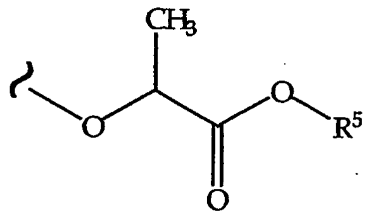

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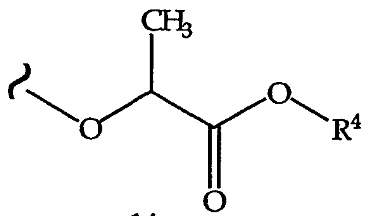

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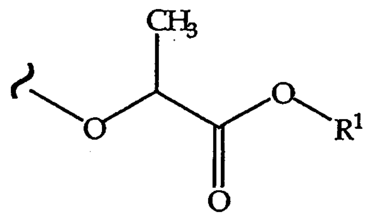

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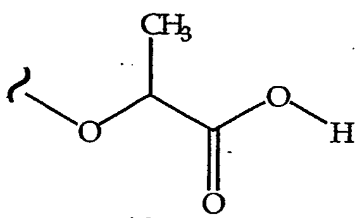

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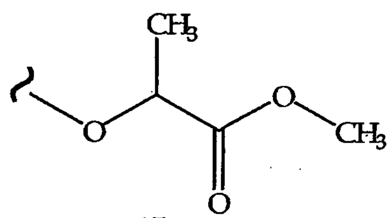

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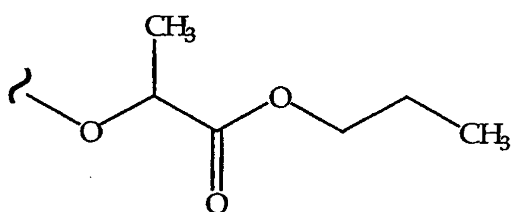

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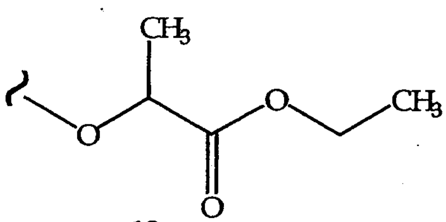

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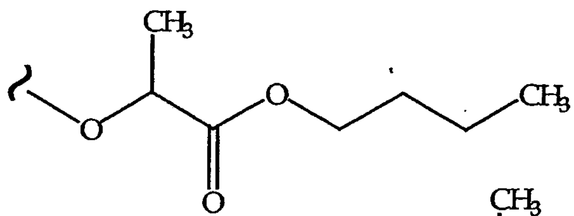

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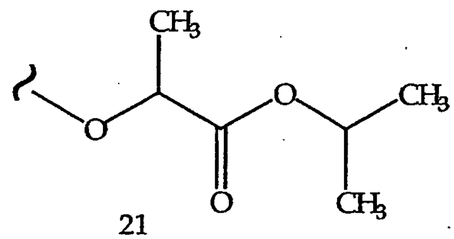

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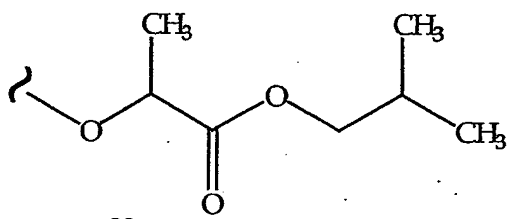

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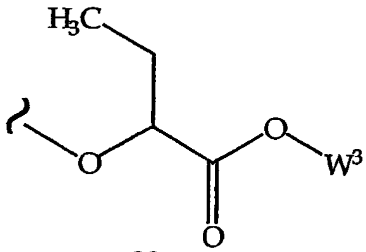

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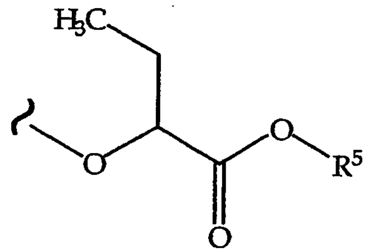

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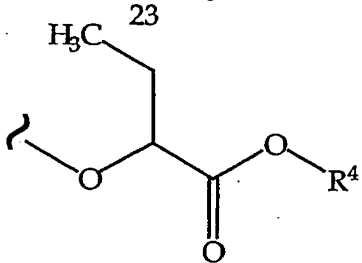

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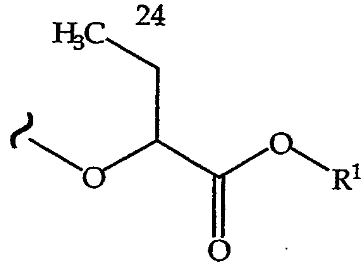

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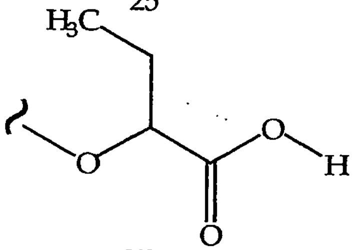

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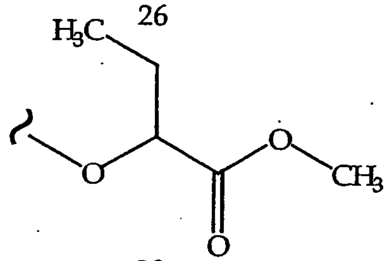

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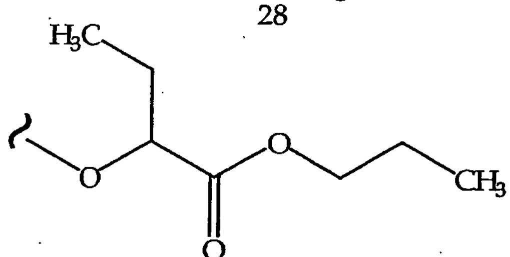

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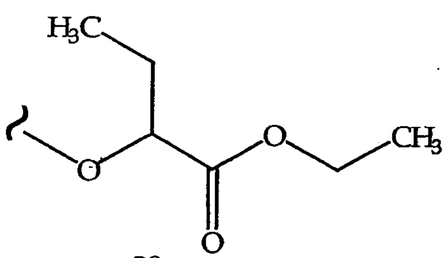

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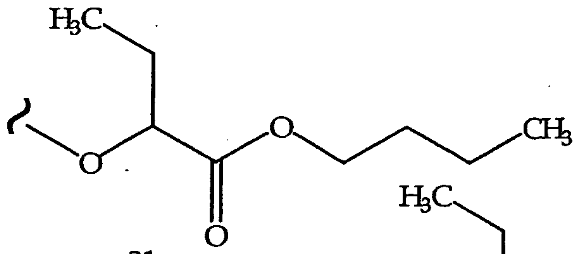

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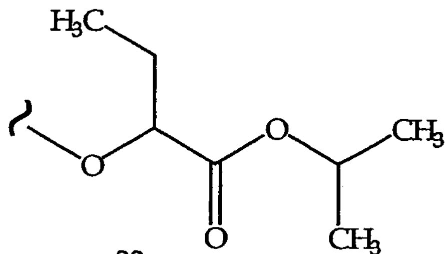

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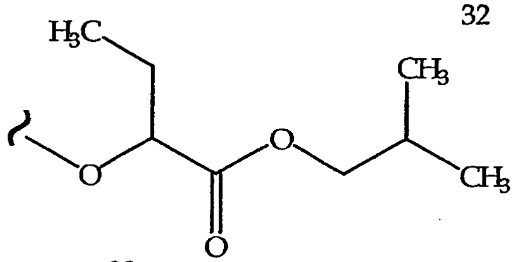

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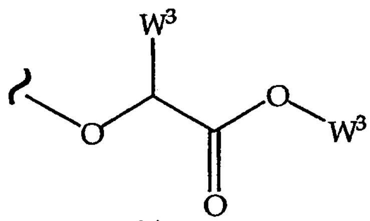

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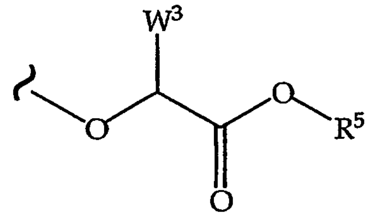

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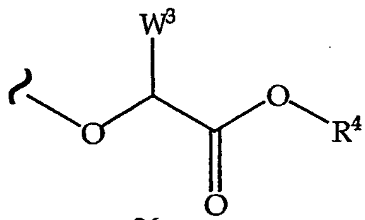

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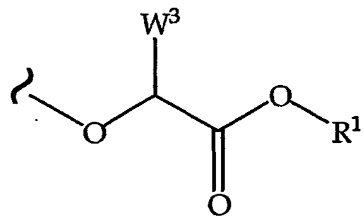

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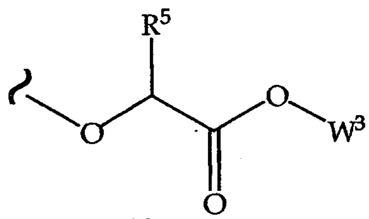

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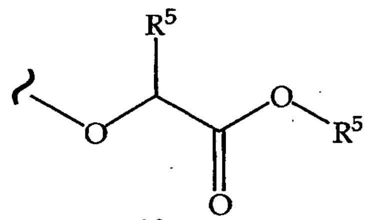

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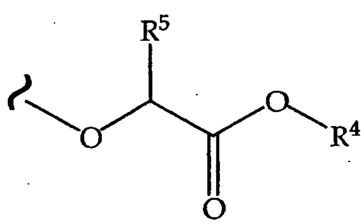

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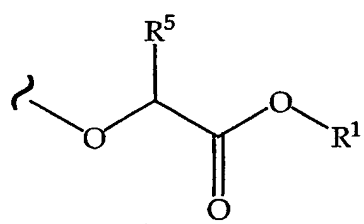

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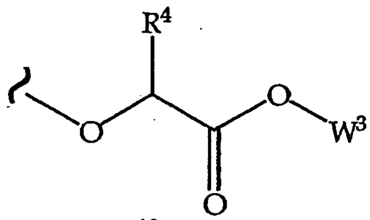

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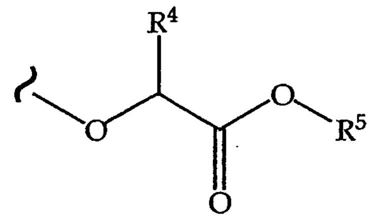

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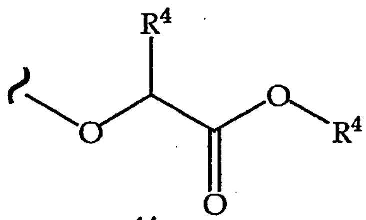

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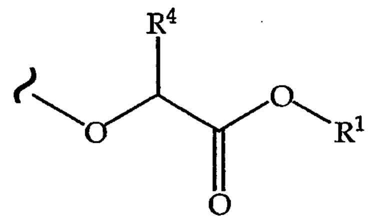

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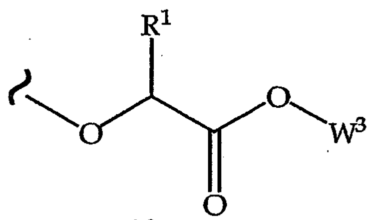

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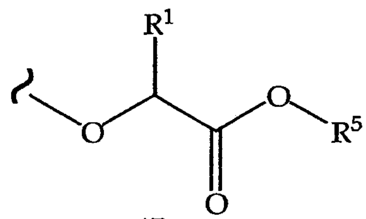

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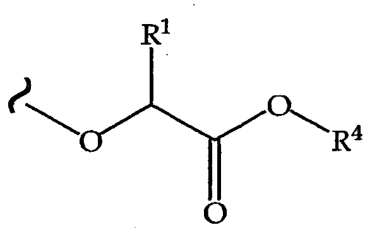

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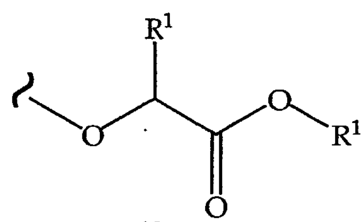

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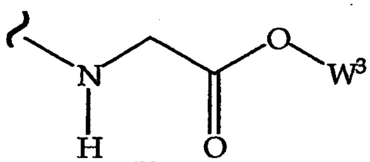
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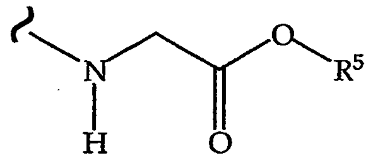
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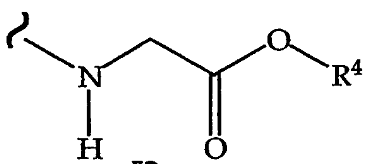
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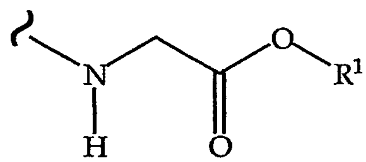
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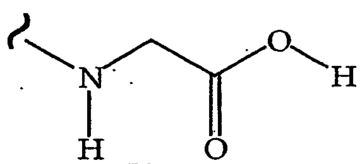
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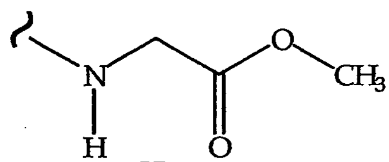
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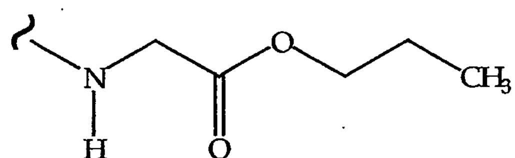
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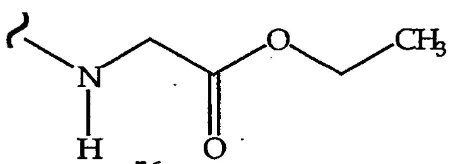
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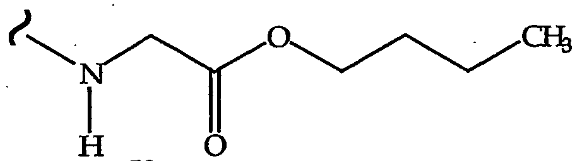

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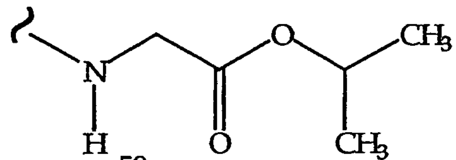

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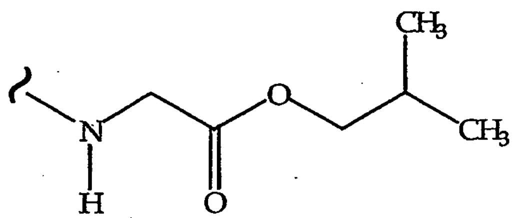

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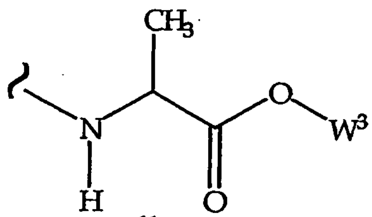
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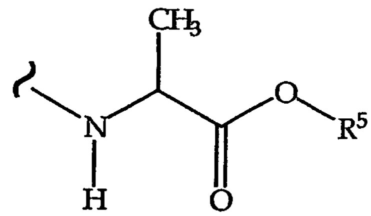
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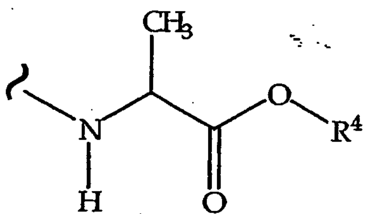
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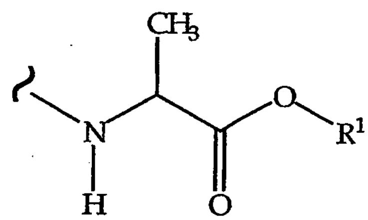
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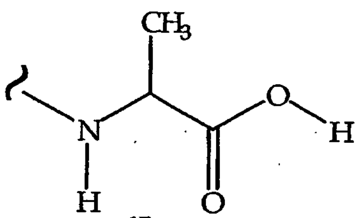
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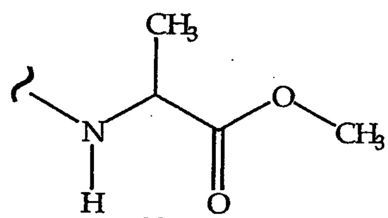
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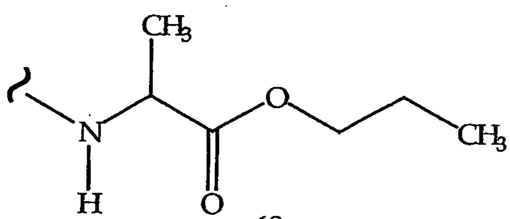
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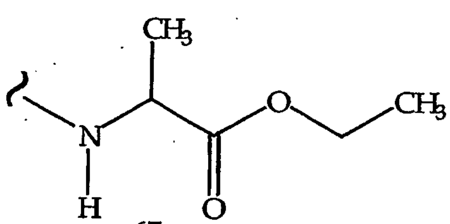
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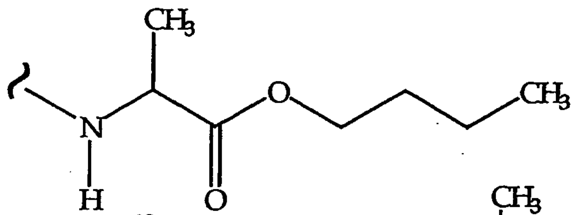

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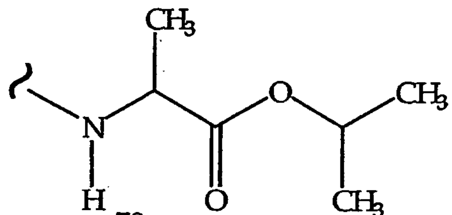

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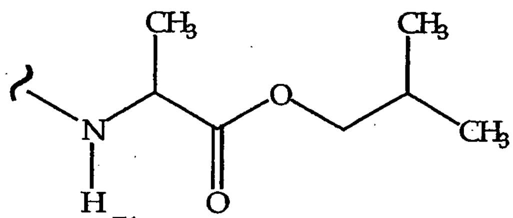

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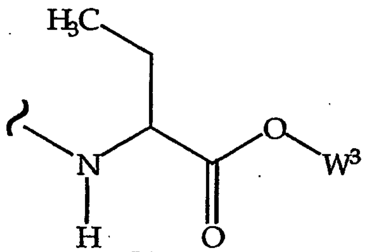
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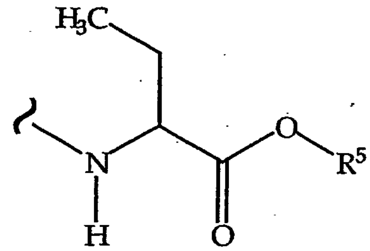
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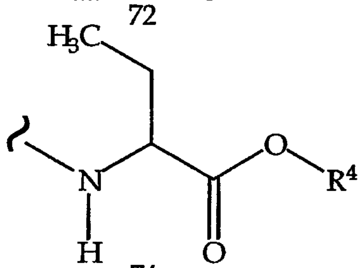
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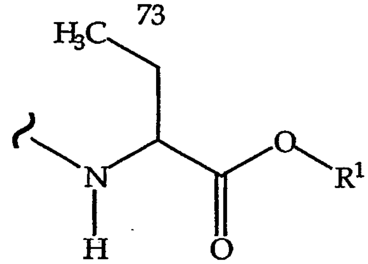
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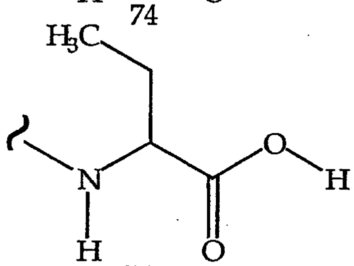
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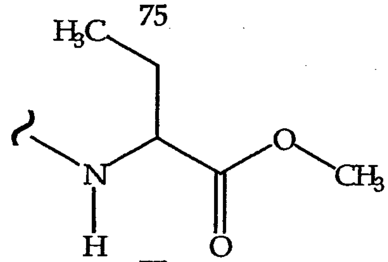
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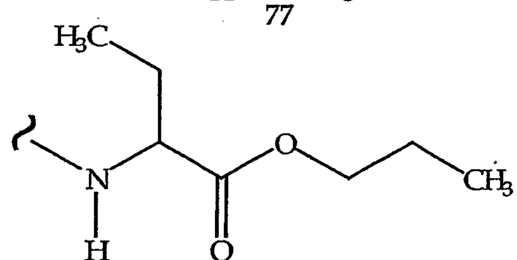
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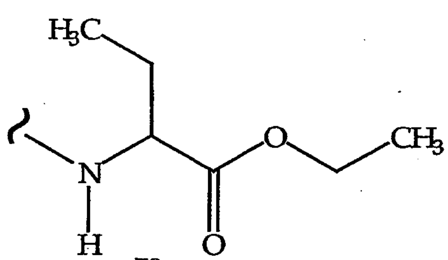
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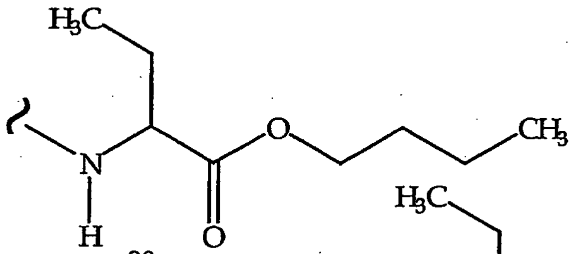

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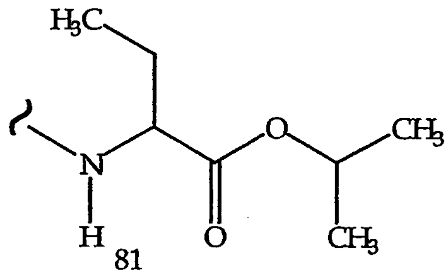

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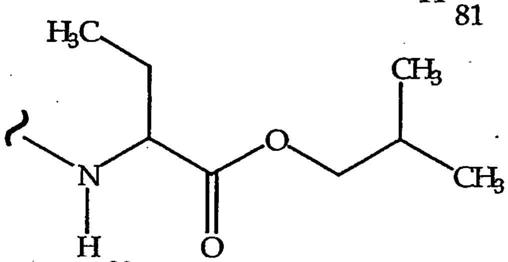

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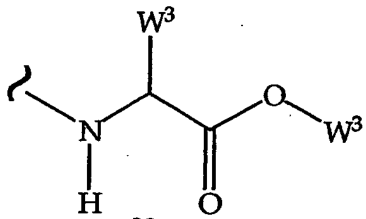

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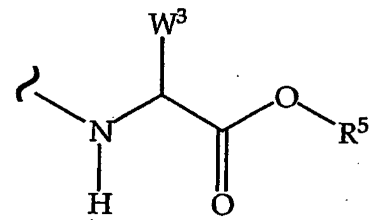

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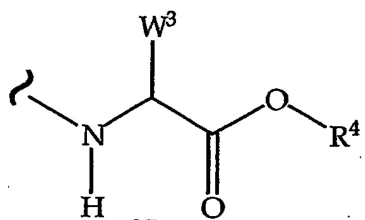

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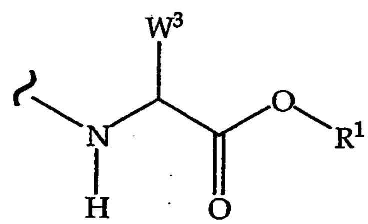

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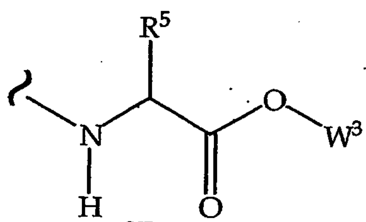

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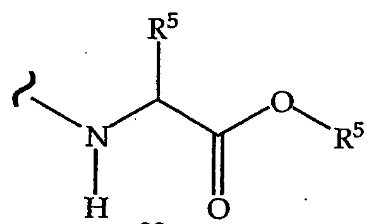

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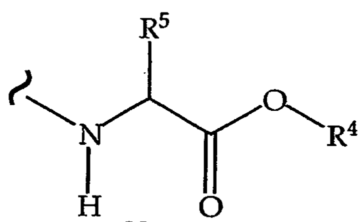

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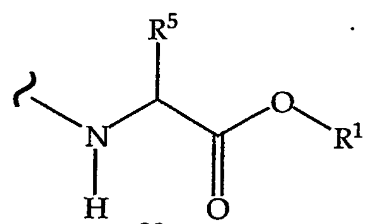

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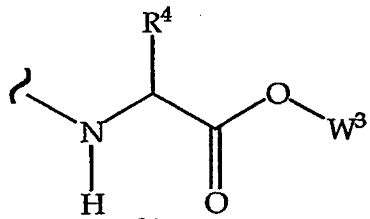
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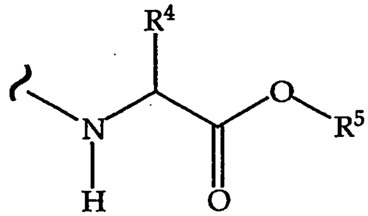
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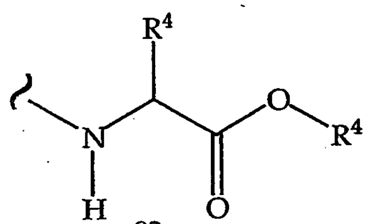
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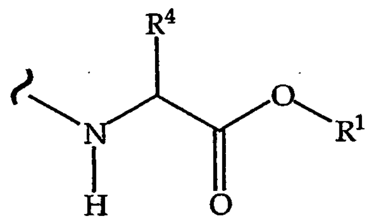
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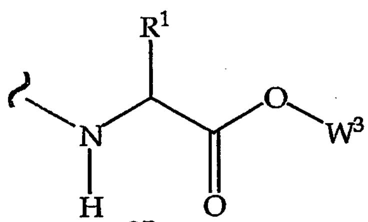
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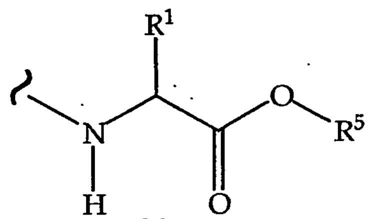
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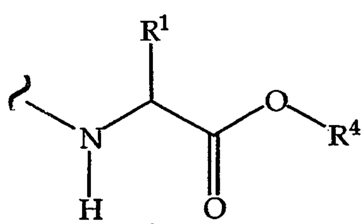
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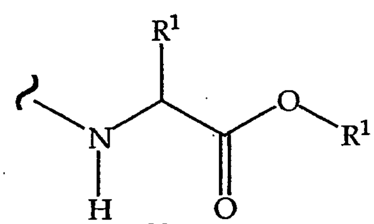
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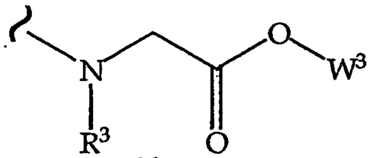

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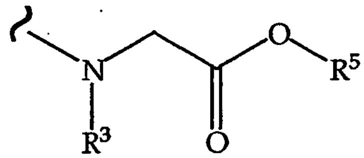

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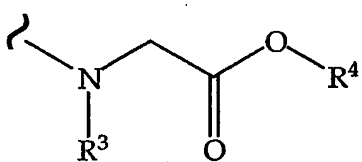

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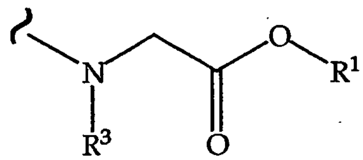

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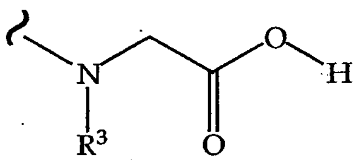

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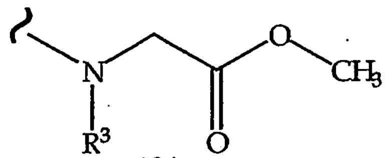

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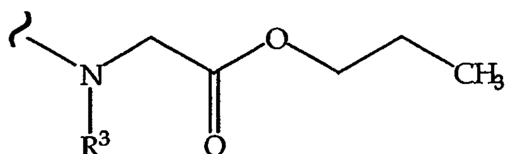

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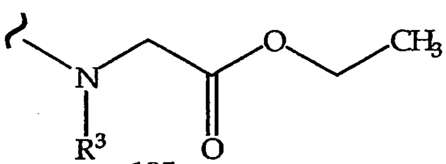

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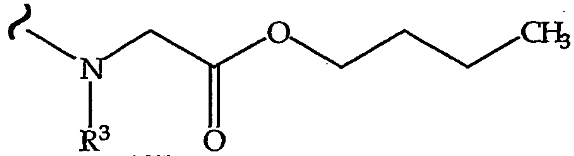

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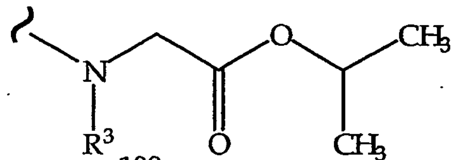

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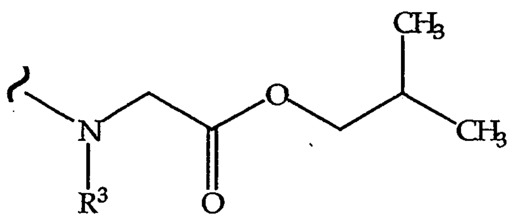

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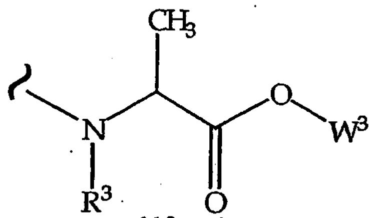

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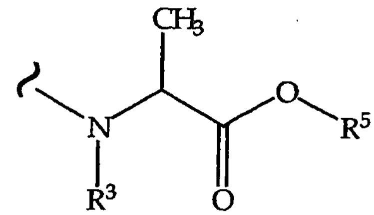

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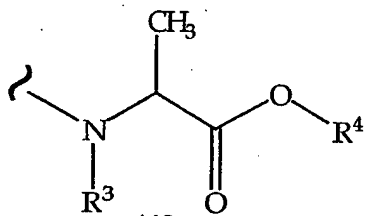

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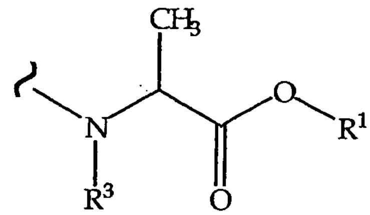

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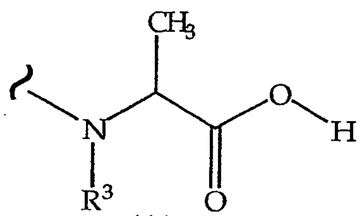

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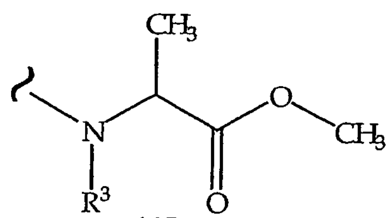

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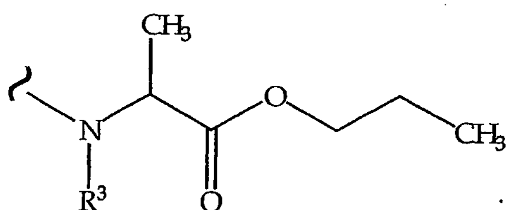

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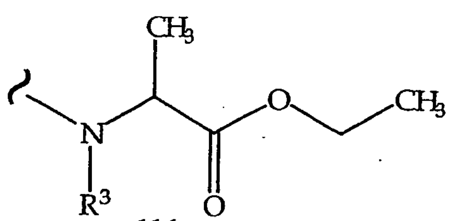

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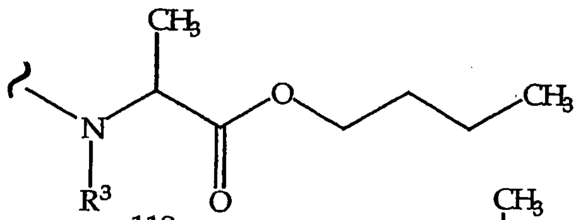

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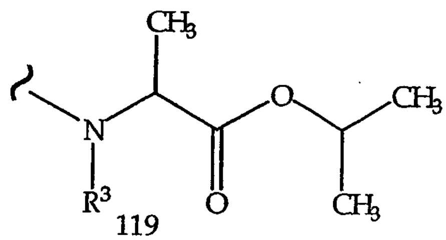

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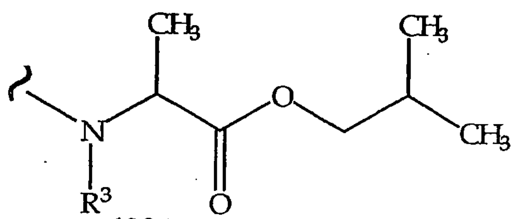

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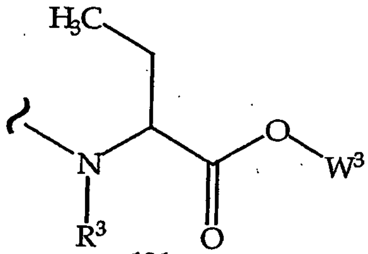

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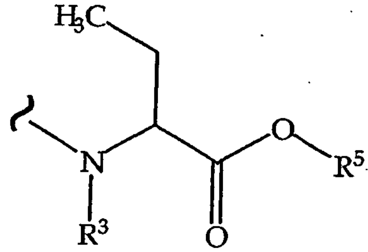

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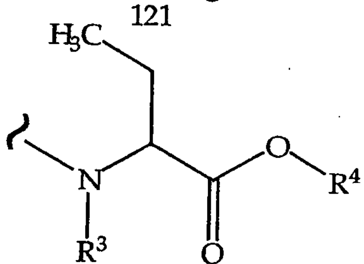

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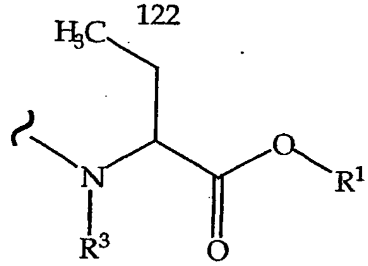

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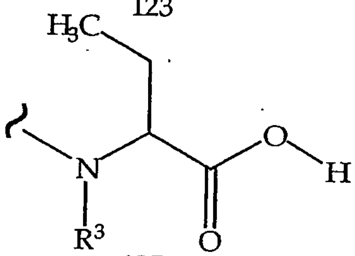

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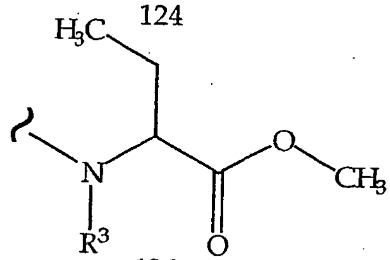

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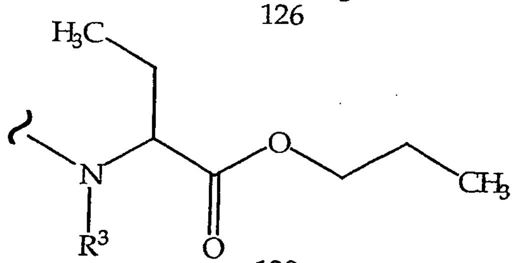

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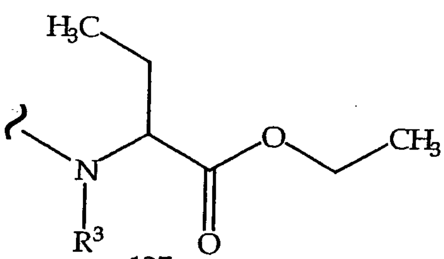

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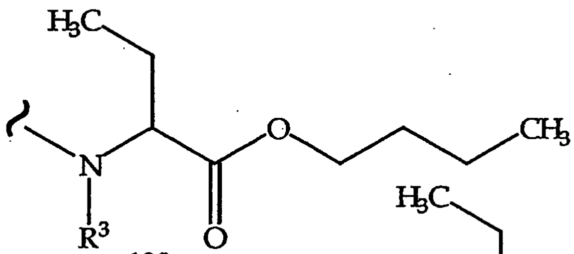

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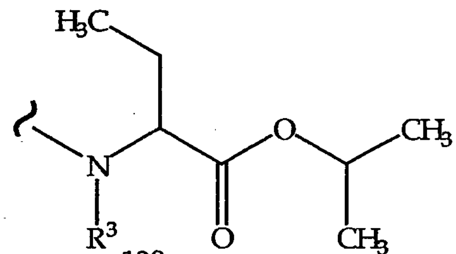

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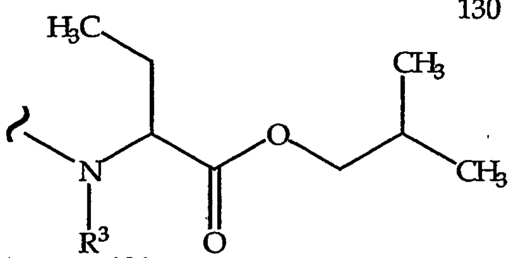

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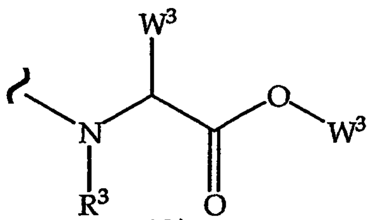

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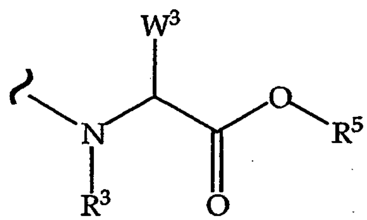

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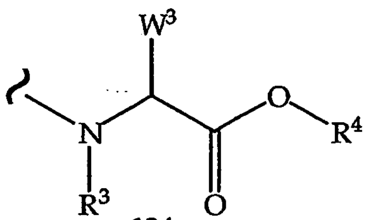

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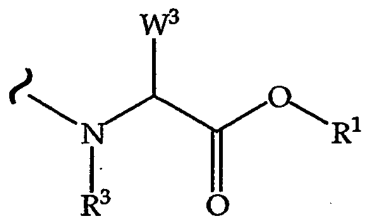

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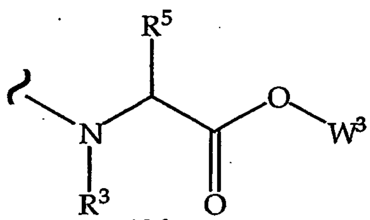

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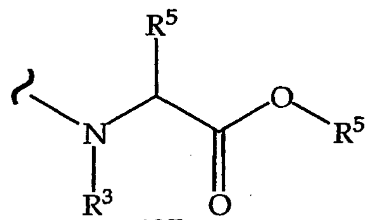

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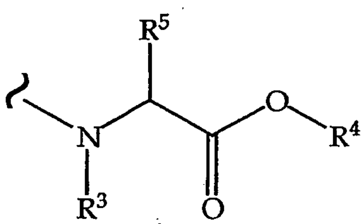

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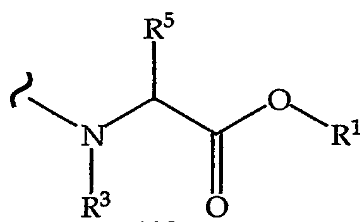

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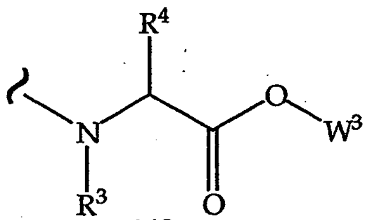
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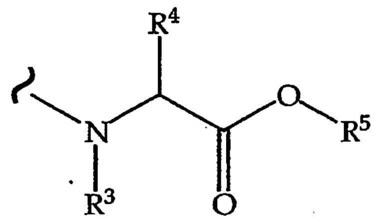
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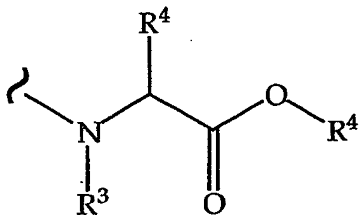
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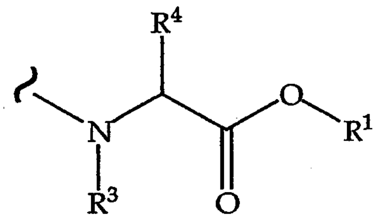
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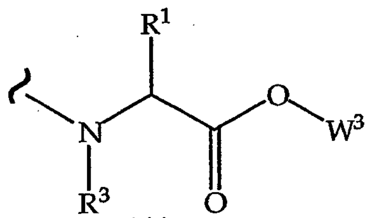
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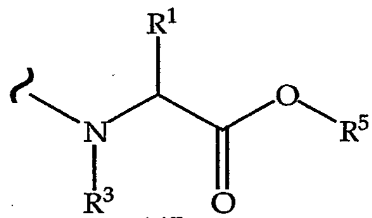
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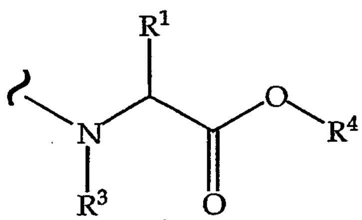
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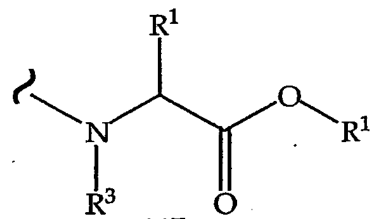
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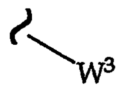

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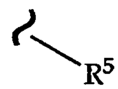

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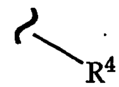

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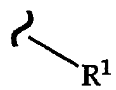

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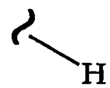

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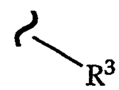

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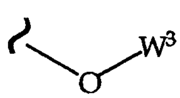

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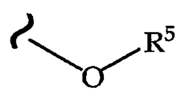

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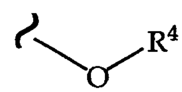

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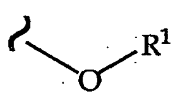

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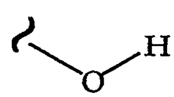

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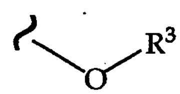

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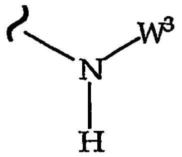
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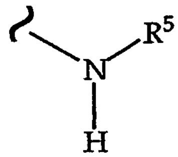
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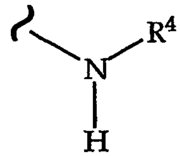
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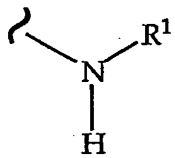
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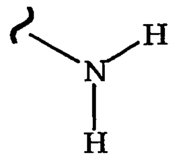
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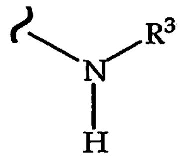
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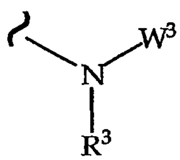
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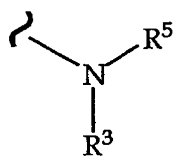
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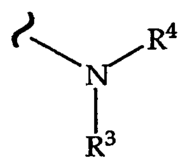
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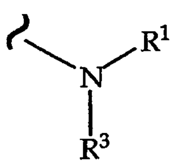
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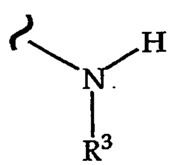
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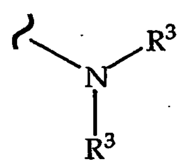
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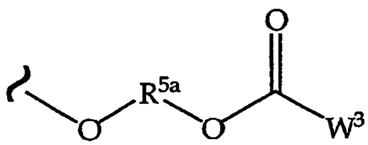

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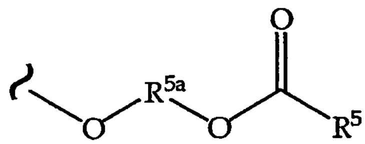

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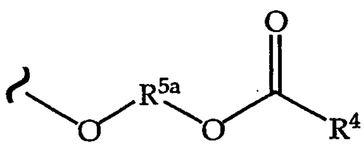

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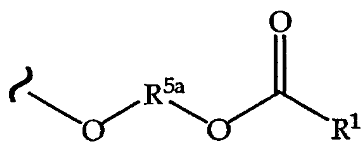

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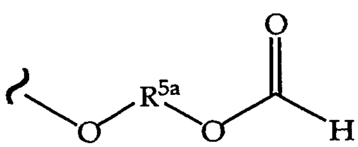

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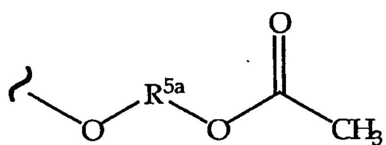

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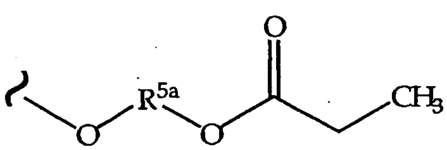

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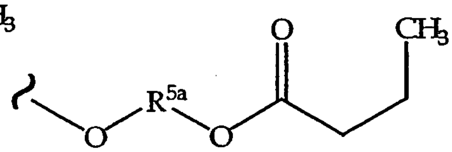

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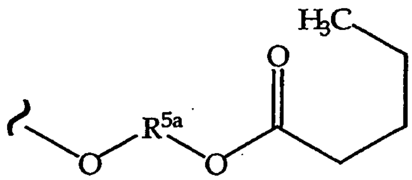

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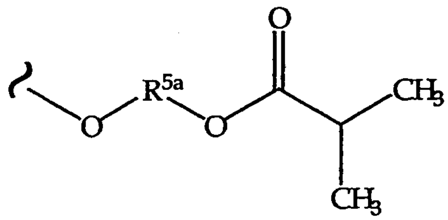

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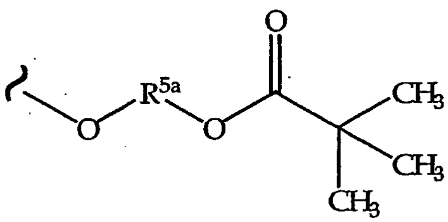

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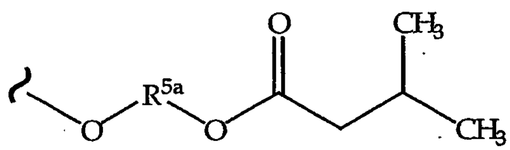

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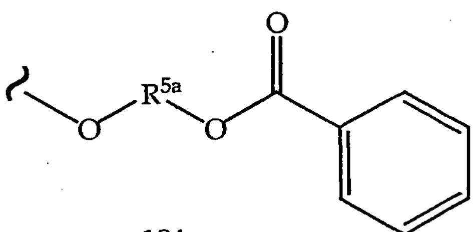

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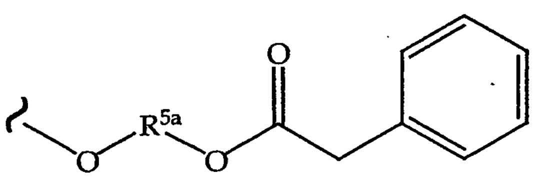

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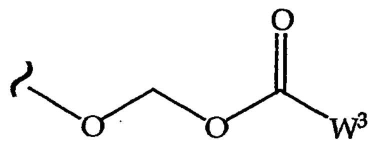

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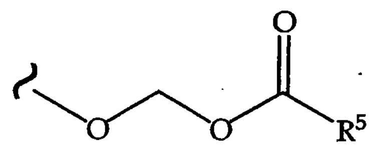

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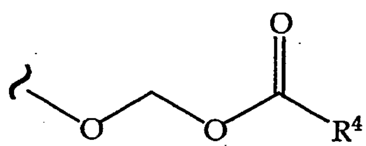

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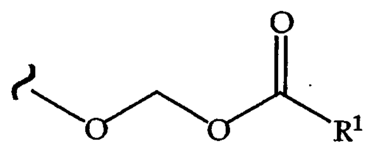

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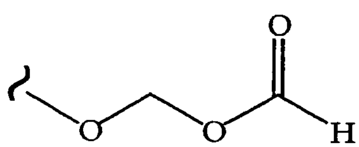

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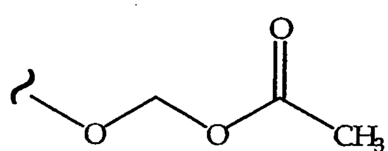

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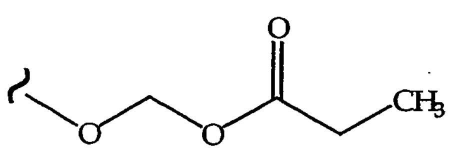

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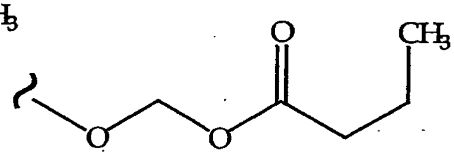

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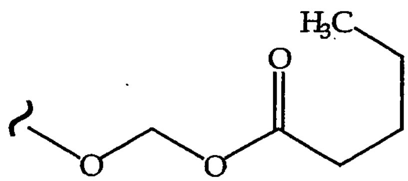

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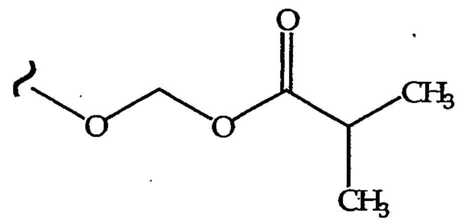

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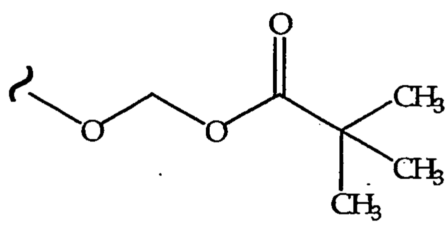

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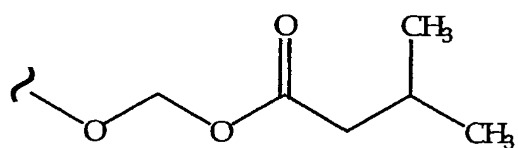

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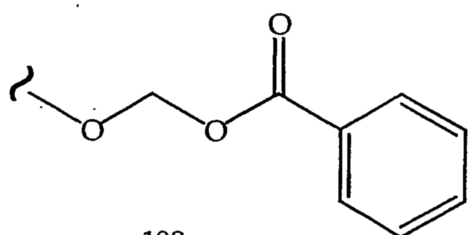

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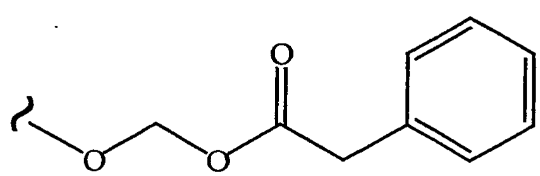

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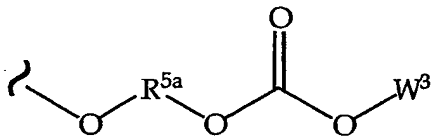

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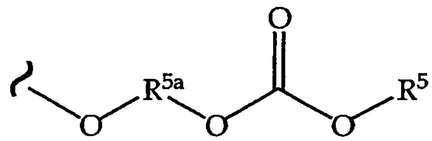

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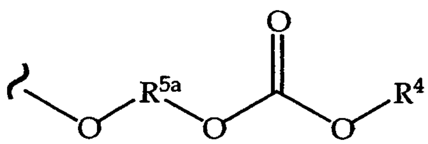

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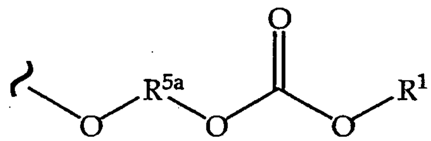

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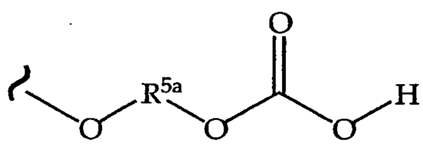

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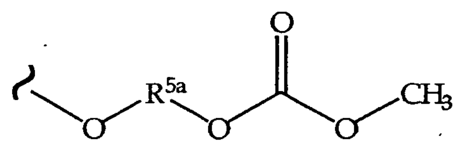

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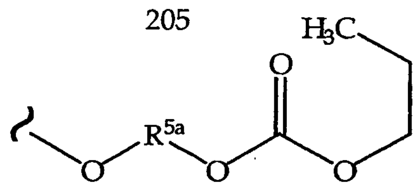

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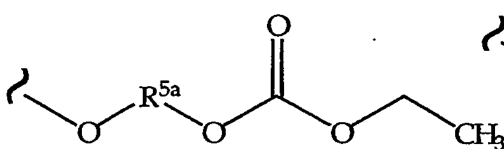

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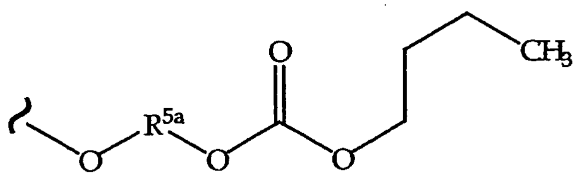

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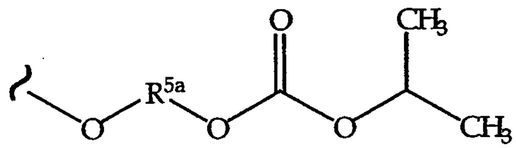

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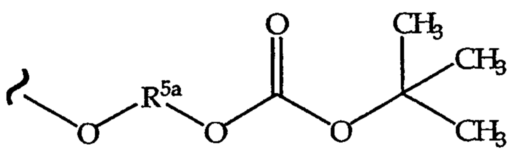

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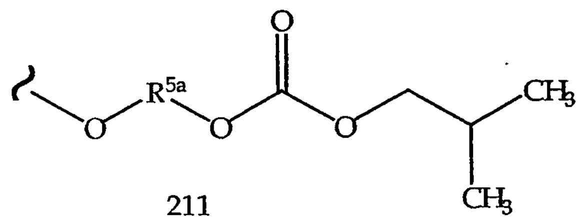

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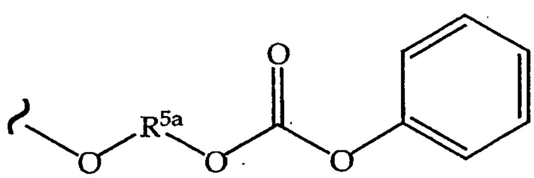

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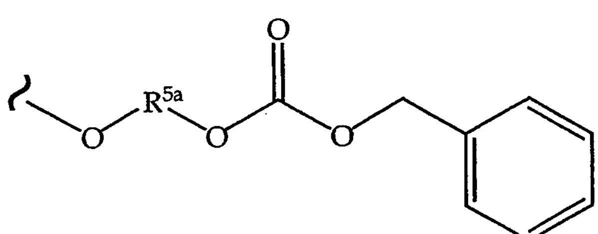

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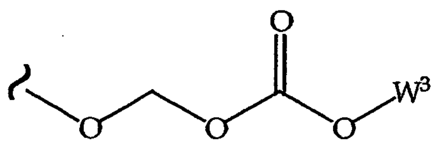

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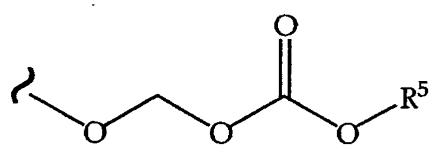

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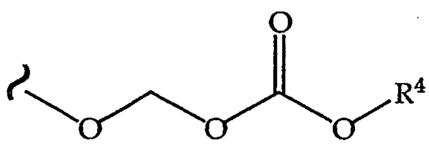

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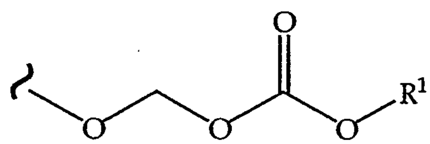

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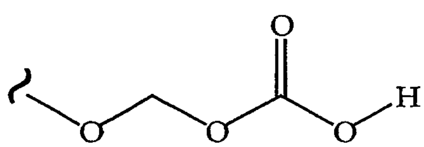

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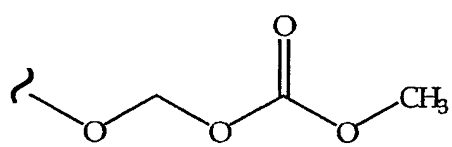

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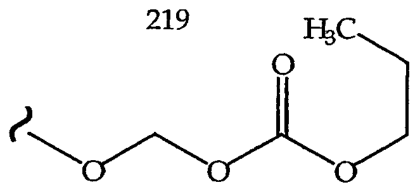

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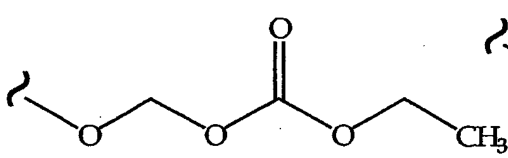

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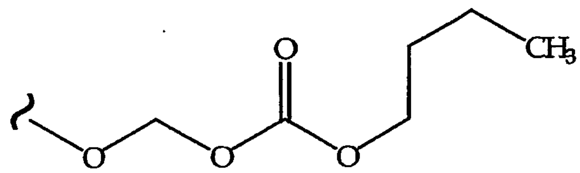

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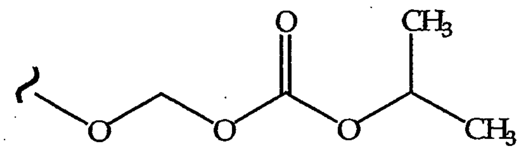

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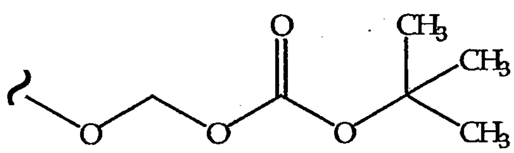

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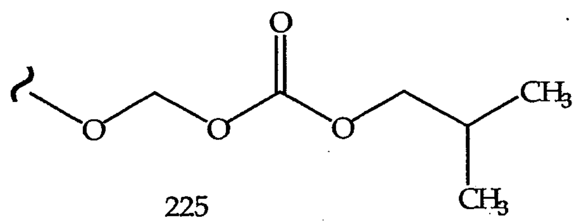

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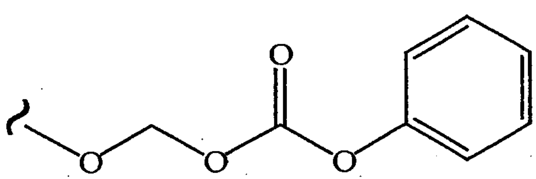

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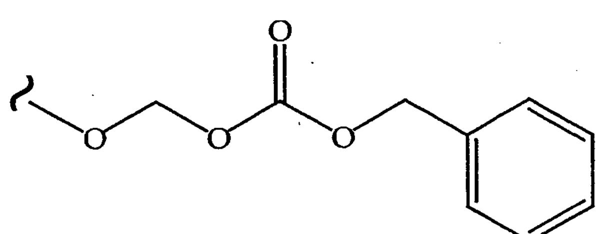

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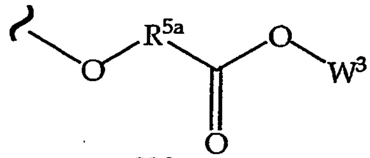
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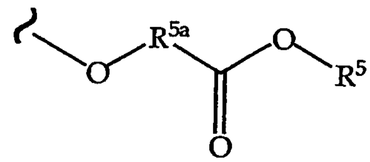
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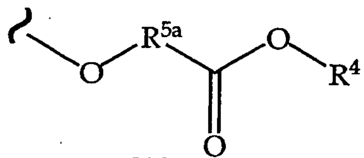
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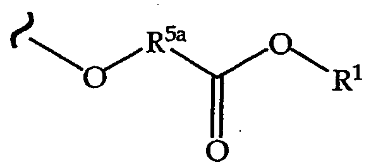
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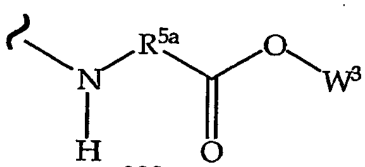
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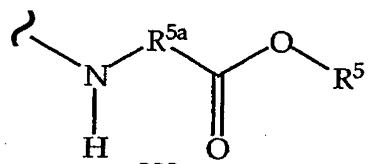
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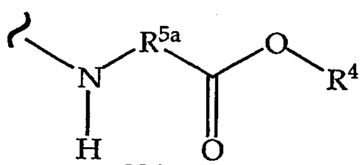
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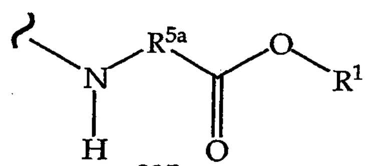
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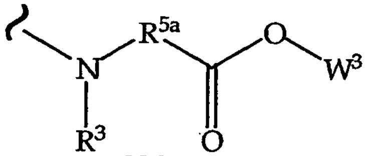

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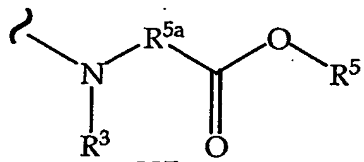

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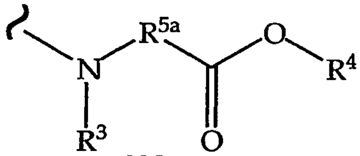

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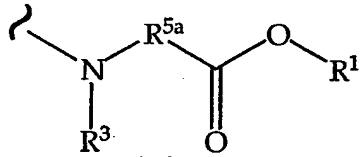

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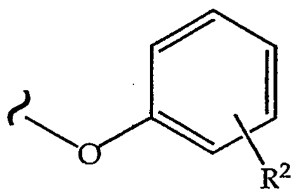

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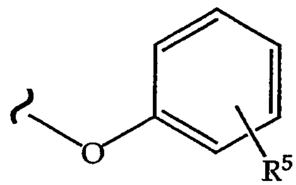

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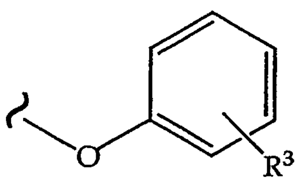

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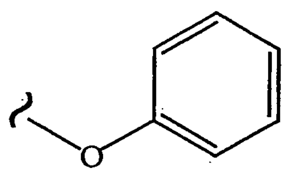

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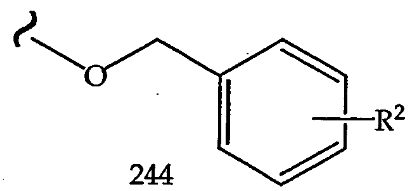

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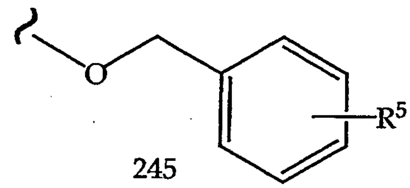

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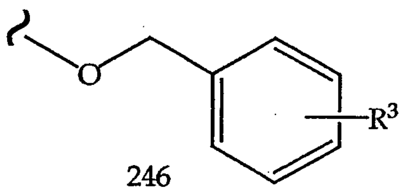

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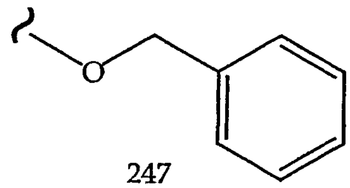

247

Table 100

Prodrugs of 1.B

1.B.228.228; 1.B.228.229; 1.B.228.230; 1.B.228.231; 1.B.228.236; 1.B.228.237; 1.B.228.238; 1.B.228.239; 1.B.228.154; 1.B.228.157; 1.B.228.166; 1.B.228.169; 1.B.228.172; 1.B.228.175; 1.B.228.240; 1.B.228.244; 1.B.229.228; 1.B.229.229; 1.B.229.230; 1.B.229.231; 1.B.229.236; 1.B.229.237; 1.B.229.238; 1.B.229.239; 1.B.229.154; 1.B.229.157; 1.B.229.166; 1.B.229.169; 1.B.229.172; 1.B.229.175; 1.B.229.240; 1.B.229.244; 1.B.230.228; 1.B.230.229; 1.B.230.230; 1.B.230.231; 1.B.230.236; 1.B.230.237; 1.B.230.238; 1.B.230.239; 1.B.230.154; 1.B.230.157; 1.B.230.166; 1.B.230.169; 1.B.230.172; 1.B.230.175; 1.B.230.240; 1.B.230.244; 1.B.231.228; 1.B.231.229; 1.B.231.230; 1.B.231.231; 1.B.231.236; 1.B.231.237; 1.B.231.238; 1.B.231.239; 1.B.231.154; 1.B.231.157; 1.B.231.166; 1.B.231.169; 1.B.231.172; 1.B.231.175; 1.B.231.240; 1.B.231.244; 1.B.236.228; 1.B.236.229; 1.B.236.230; 1.B.236.231; 1.B.236.236; 1.B.236.237; 1.B.236.238; 1.B.236.239; 1.B.236.154; 1.B.236.157; 1.B.236.166; 1.B.236.169; 1.B.236.172; 1.B.236.175; 1.B.236.240; 1.B.236.244; 1.B.237.228; 1.B.237.229; 1.B.237.230; 1.B.237.231; 1.B.237.236; 1.B.237.237; 1.B.237.238; 1.B.237.239; 1.B.237.154; 1.B.237.157; 1.B.237.166; 1.B.237.169; 1.B.237.172; 1.B.237.175; 1.B.237.240; 1.B.237.244; 1.B.238.228; 1.B.238.229; 1.B.238.230; 1.B.238.231; 1.B.238.236; 1.B.238.237; 1.B.238.238; 1.B.238.239; 1.B.238.154; 1.B.238.157; 1.B.238.166; 1.B.238.169; 1.B.238.172; 1.B.238.175; 1.B.238.240; 1.B.238.244; 1.B.239.228; 1.B.239.229; 1.B.239.230; 1.B.239.231; 1.B.239.236; 1.B.239.237; 1.B.239.238; 1.B.239.239; 1.B.239.154; 1.B.239.157; 1.B.239.166; 1.B.239.169; 1.B.239.172; 1.B.239.175; 1.B.239.240; 1.B.239.244; 1.B.154.228; 1.B.154.229; 1.B.154.230; 1.B.154.231; 1.B.154.236; 1.B.154.237; 1.B.154.238; 1.B.154.239; 1.B.154.154; 1.B.154.157; 1.B.154.166; 1.B.154.169; 1.B.154.172; 1.B.154.175; 1.B.154.240; 1.B.154.244; 1.B.157.228; 1.B.157.229; 1.B.157.230; 1.B.157.231; 1.B.157.236; 1.B.157.237; 1.B.157.238; 1.B.157.239; 1.B.157.154; 1.B.157.157; 1.B.157.166; 1.B.157.169; 1.B.157.172; 1.B.157.175; 1.B.157.240; 1.B.157.244; 1.B.166.228; 1.B.166.229; 1.B.166.230; 1.B.166.231; 1.B.166.236; 1.B.166.237; 1.B.166.238; 1.B.166.239; 1.B.166.154; 1.B.166.157; 1.B.166.166; 1.B.166.169; 1.B.166.172; 1.B.166.175; 1.B.166.240; 1.B.166.244; 1.B.169.228; 1.B.169.229; 1.B.169.230; 1.B.169.231; 1.B.169.236; 1.B.169.237; 1.B.169.238; 1.B.169.239; 1.B.169.154; 1.B.169.157; 1.B.169.166; 1.B.169.169; 1.B.169.172; 1.B.169.175; 1.B.169.240; 1.B.169.244; 1.B.172.228; 1.B.172.229; 1.B.172.230; 1.B.172.231; 1.B.172.236; 1.B.172.237; 1.B.172.238; 1.B.172.239; 1.B.172.154; 1.B.172.157; 1.B.172.166; 1.B.172.169; 1.B.172.172; 1.B.172.175; 1.B.172.240; 1.B.172.244; 1.B.175.228; 1.B.175.229; 1.B.175.230; 1.B.175.231; 1.B.175.236; 1.B.175.237; 1.B.175.238; 1.B.175.239; 1.B.175.154; 1.B.175.157; 1.B.175.166; 1.B.175.169; 1.B.175.172; 1.B.175.175; 1.B.175.240; 1.B.175.244; 1.B.240.228; 1.B.240.229; 1.B.240.230; 1.B.240.231; 1.B.240.236; 1.B.240.237; 1.B.240.238; 1.B.240.239; 1.B.240.154; 1.B.240.157; 1.B.240.166; 1.B.240.169; 1.B.240.172; 1.B.240.175; 1.B.240.240; 1.B.240.244; 1.B.244.228; 1.B.244.229; 1.B.244.230; 1.B.244.231; 1.B.244.236; 1.B.244.237; 1.B.244.238; 1.B.244.239; 1.B.244.154; 1.B.244.157; 1.B.244.166; 1.B.244.169; 1.B.244.172; 1.B.244.175; 1.B.244.240; 1.B.244.244;

Prodrugs of 1.D

1.D.228.228; 1.D.228.229; 1.D.228.230; 1.D.228.231; 1.D.228.236; 1.D.228.237; 1.D.228.238; 1.D.228.239; 1.D.228.154; 1.D.228.157; 1.D.228.166; 1.D.228.169; 1.D.228.172; 1.D.228.175; 1.D.228.240; 1.D.228.244; 1.D.229.228; 1.D.229.229; 1.D.229.230; 1.D.229.231; 1.D.229.236; 1.D.229.237; 1.D.229.238; 1.D.229.239;

1.D.229.154; 1.D.229.157; 1.D.229.166; 1.D.229.169; 1.D.229.172; 1.D.229.175; 1.D.229.240; 1.D.229.244; 1.D.230.228; 1.D.230.229; 1.D.230.230; 1.D.230.231; 1.D.230.236; 1.D.230.237; 1.D.230.238; 1.D.230.239; 1.D.230.154; 1.D.230.157; 1.D.230.166; 1.D.230.169; 1.D.230.172; 1.D.230.175; 1.D.230.240; 1.D.230.244; 1.D.231.228; 1.D.231.229; 1.D.231.230; 1.D.231.231; 1.D.231.236; 1.D.231.237; 1.D.231.238; 1.D.231.239; 1.D.231.154; 1.D.231.157; 1.D.231.166; 1.D.231.169; 1.D.231.172; 1.D.231.175; 1.D.231.240; 1.D.231.244; 1.D.236.228; 1.D.236.229; 1.D.236.230; 1.D.236.231; 1.D.236.236; 1.D.236.237; 1.D.236.238; 1.D.236.239; 1.D.236.154; 1.D.236.157; 1.D.236.166; 1.D.236.169; 1.D.236.172; 1.D.236.175; 1.D.236.240; 1.D.236.244; 1.D.237.228; 1.D.237.229; 1.D.237.230; 1.D.237.231; 1.D.237.236; 1.D.237.237; 1.D.237.238; 1.D.237.239; 1.D.237.154; 1.D.237.157; 1.D.237.166; 1.D.237.169; 1.D.237.172; 1.D.237.175; 1.D.237.240; 1.D.237.244; 1.D.238.228; 1.D.238.229; 1.D.238.230; 1.D.238.231; 1.D.238.236; 1.D.238.237; 1.D.238.238; 1.D.238.239; 1.D.238.154; 1.D.238.157; 1.D.238.166; 1.D.238.169; 1.D.238.172; 1.D.238.175; 1.D.238.240; 1.D.238.244; 1.D.239.228; 1.D.239.229; 1.D.239.230; 1.D.239.231; 1.D.239.236; 1.D.239.237; 1.D.239.238; 1.D.239.239; 1.D.239.154; 1.D.239.157; 1.D.239.166; 1.D.239.169; 1.D.239.172; 1.D.239.175; 1.D.239.240; 1.D.239.244; 1.D.154.228; 1.D.154.229; 1.D.154.230; 1.D.154.231; 1.D.154.236; 1.D.154.237; 1.D.154.238; 1.D.154.239; 1.D.154.154; 1.D.154.157; 1.D.154.166; 1.D.154.169; 1.D.154.172; 1.D.154.175; 1.D.154.240; 1.D.154.244; 1.D.157.228; 1.D.157.229; 1.D.157.230; 1.D.157.231; 1.D.157.236; 1.D.157.237; 1.D.157.238; 1.D.157.239; 1.D.157.154; 1.D.157.157; 1.D.157.166; 1.D.157.169; 1.D.157.172; 1.D.157.175; 1.D.157.240; 1.D.157.244; 1.D.166.228; 1.D.166.229; 1.D.166.230; 1.D.166.231; 1.D.166.236; 1.D.166.237; 1.D.166.238; 1.D.166.239; 1.D.166.154; 1.D.166.157; 1.D.166.166; 1.D.166.169; 1.D.166.172; 1.D.166.175; 1.D.166.240; 1.D.166.244; 1.D.169.228; 1.D.169.229; 1.D.169.230; 1.D.169.231; 1.D.169.236; 1.D.169.237; 1.D.169.238; 1.D.169.239; 1.D.169.154; 1.D.169.157; 1.D.169.166; 1.D.169.169; 1.D.169.172; 1.D.169.175; 1.D.169.240; 1.D.169.244; 1.D.172.228; 1.D.172.229; 1.D.172.230; 1.D.172.231; 1.D.172.236; 1.D.172.237; 1.D.172.238; 1.D.172.239; 1.D.172.154; 1.D.172.157; 1.D.172.166; 1.D.172.169; 1.D.172.172; 1.D.172.175; 1.D.172.240; 1.D.172.244; 1.D.175.228; 1.D.175.229; 1.D.175.230; 1.D.175.231; 1.D.175.236; 1.D.175.237; 1.D.175.238; 1.D.175.239; 1.D.175.154; 1.D.175.157; 1.D.175.166; 1.D.175.169; 1.D.175.172; 1.D.175.175; 1.D.175.240; 1.D.175.244; 1.D.240.228; 1.D.240.229; 1.D.240.230; 1.D.240.231; 1.D.240.236; 1.D.240.237; 1.D.240.238; 1.D.240.239; 1.D.240.154; 1.D.240.157; 1.D.240.166; 1.D.240.169; 1.D.240.172; 1.D.240.175; 1.D.240.240; 1.D.240.244; 1.D.244.228; 1.D.244.229; 1.D.244.230; 1.D.244.231; 1.D.244.236; 1.D.244.237; 1.D.244.238; 1.D.244.239; 1.D.244.154; 1.D.244.157; 1.D.244.166; 1.D.244.169; 1.D.244.172; 1.D.244.175; 1.D.244.240; 1.D.244.244;

Prodrugs of 1.E

1.E.228.228; 1.E.228.229; 1.E.228.230; 1.E.228.231; 1.E.228.236; 1.E.228.237; 1.E.228.238; 1.E.228.239; 1.E.228.154; 1.E.228.157; 1.E.228.166; 1.E.228.169; 1.E.228.172; 1.E.228.175; 1.E.228.240; 1.E.228.244; 1.E.229.228; 1.E.229.229; 1.E.229.230; 1.E.229.231; 1.E.229.236; 1.E.229.237; 1.E.229.238; 1.E.229.239; 1.E.229.154; 1.E.229.157; 1.E.229.166; 1.E.229.169; 1.E.229.172; 1.E.229.175; 1.E.229.240; 1.E.229.244; 1.E.230.228; 1.E.230.229;

1.E.230.230; 1.E.230.231; 1.E.230.236; 1.E.230.237; 1.E.230.238; 1.E.230.239; 1.E.230.154; 1.E.230.157; 1.E.230.166; 1.E.230.169; 1.E.230.172; 1.E.230.175; 1.E.230.240; 1.E.230.244; 1.E.231.228; 1.E.231.229; 1.E.231.230; 1.E.231.231; 1.E.231.236; 1.E.231.237; 1.E.231.238; 1.E.231.239; 1.E.231.154; 1.E.231.157; 1.E.231.166; 1.E.231.169; 1.E.231.172; 1.E.231.175; 1.E.231.240; 1.E.231.244; 1.E.236.228; 1.E.236.229; 1.E.236.230; 1.E.236.231; 1.E.236.236; 1.E.236.237; 1.E.236.238; 1.E.236.239; 1.E.236.154; 1.E.236.157; 1.E.236.166; 1.E.236.169; 1.E.236.172; 1.E.236.175; 1.E.236.240; 1.E.236.244; 1.E.237.228; 1.E.237.229; 1.E.237.230; 1.E.237.231; 1.E.237.236; 1.E.237.237; 1.E.237.238; 1.E.237.239; 1.E.237.154; 1.E.237.157; 1.E.237.166; 1.E.237.169; 1.E.237.172; 1.E.237.175; 1.E.237.240; 1.E.237.244; 1.E.238.228; 1.E.238.229; 1.E.238.230; 1.E.238.231; 1.E.238.236; 1.E.238.237; 1.E.238.238; 1.E.238.239; 1.E.238.154; 1.E.238.157; 1.E.238.166; 1.E.238.169; 1.E.238.172; 1.E.238.175; 1.E.238.240; 1.E.238.244; 1.E.239.228; 1.E.239.229; 1.E.239.230; 1.E.239.231; 1.E.239.236; 1.E.239.237; 1.E.239.238; 1.E.239.239; 1.E.239.154; 1.E.239.157; 1.E.239.166; 1.E.239.169; 1.E.239.172; 1.E.239.175; 1.E.239.240; 1.E.239.244; 1.E.154.228; 1.E.154.229; 1.E.154.230; 1.E.154.231; 1.E.154.236; 1.E.154.237; 1.E.154.238; 1.E.154.239; 1.E.154.154; 1.E.154.157; 1.E.154.166; 1.E.154.169; 1.E.154.172; 1.E.154.175; 1.E.154.240; 1.E.154.244; 1.E.157.228; 1.E.157.229; 1.E.157.230; 1.E.157.231; 1.E.157.236; 1.E.157.237; 1.E.157.238; 1.E.157.239; 1.E.157.154; 1.E.157.157; 1.E.157.166; 1.E.157.169; 1.E.157.172; 1.E.157.175; 1.E.157.240; 1.E.157.244; 1.E.166.228; 1.E.166.229; 1.E.166.230; 1.E.166.231; 1.E.166.236; 1.E.166.237; 1.E.166.238; 1.E.166.239; 1.E.166.154; 1.E.166.157; 1.E.166.166; 1.E.166.169; 1.E.166.172; 1.E.166.175; 1.E.166.240; 1.E.166.244; 1.E.169.228; 1.E.169.229; 1.E.169.230; 1.E.169.231; 1.E.169.236; 1.E.169.237; 1.E.169.238; 1.E.169.239; 1.E.169.154; 1.E.169.157; 1.E.169.166; 1.E.169.169; 1.E.169.172; 1.E.169.175; 1.E.169.240; 1.E.169.244; 1.E.172.228; 1.E.172.229; 1.E.172.230; 1.E.172.231; 1.E.172.236; 1.E.172.237; 1.E.172.238; 1.E.172.239; 1.E.172.154; 1.E.172.157; 1.E.172.166; 1.E.172.169; 1.E.172.172; 1.E.172.175; 1.E.172.240; 1.E.172.244; 1.E.175.228; 1.E.175.229; 1.E.175.230; 1.E.175.231; 1.E.175.236; 1.E.175.237; 1.E.175.238; 1.E.175.239; 1.E.175.154; 1.E.175.157; 1.E.175.166; 1.E.175.169; 1.E.175.172; 1.E.175.175; 1.E.175.240; 1.E.175.244; 1.E.240.228; 1.E.240.229; 1.E.240.230; 1.E.240.231; 1.E.240.236; 1.E.240.237; 1.E.240.238; 1.E.240.239; 1.E.240.154; 1.E.240.157; 1.E.240.166; 1.E.240.169; 1.E.240.172; 1.E.240.175; 1.E.240.240; 1.E.240.244; 1.E.244.228; 1.E.244.229; 1.E.244.230; 1.E.244.231; 1.E.244.236; 1.E.244.237; 1.E.244.238; 1.E.244.239; 1.E.244.154; 1.E.244.157; 1.E.244.166; 1.E.244.169; 1.E.244.172; 1.E.244.175; 1.E.244.240; 1.E.244.244;

Prodrugs of 1.G

1.G.228.228; 1.G.228.229; 1.G.228.230; 1.G.228.231; 1.G.228.236; 1.G.228.237; 1.G.228.238; 1.G.228.239; 1.G.228.154; 1.G.228.157; 1.G.228.166; 1.G.228.169; 1.G.228.172; 1.G.228.175; 1.G.228.240; 1.G.228.244; 1.G.229.228; 1.G.229.229; 1.G.229.230; 1.G.229.231; 1.G.229.236; 1.G.229.237; 1.G.229.238; 1.G.229.239; 1.G.229.154; 1.G.229.157; 1.G.229.166; 1.G.229.169; 1.G.229.172; 1.G.229.175; 1.G.229.240; 1.G.229.244; 1.G.230.228; 1.G.230.229; 1.G.230.230; 1.G.230.231; 1.G.230.236; 1.G.230.237; 1.G.230.238; 1.G.230.239; 1.G.230.154; 1.G.230.157; 1.G.230.166; 1.G.230.169; 1.G.230.172; 1.G.230.175; 1.G.230.240; 1.G.230.244; 1.G.231.228; 1.G.231.229; 1.G.231.230; 1.G.231.231; 1.G.231.236; 1.G.231.237; 1.G.231.238; 1.G.231.239; 1.G.231.154; 1.G.231.157; 1.G.231.166; 1.G.231.169; 1.G.231.172; 1.G.231.175; 1.G.231.240; 1.G.231.244; 1.G.236.228; 1.G.236.229; 1.G.236.230; 1.G.236.231; 1.G.236.236; 1.G.236.237; 1.G.236.238; 1.G.236.239;

1.G.236.154; 1.G.236.157; 1.G.236.166; 1.G.236.169; 1.G.236.172; 1.G.236.175; 1.G.236.240; 1.G.236.244; 1.G.237.228; 1.G.237.229; 1.G.237.230; 1.G.237.231; 1.G.237.236; 1.G.237.237; 1.G.237.238; 1.G.237.239; 1.G.237.154; 1.G.237.157; 1.G.237.166; 1.G.237.169; 1.G.237.172; 1.G.237.175; 1.G.237.240; 1.G.237.244; 1.G.238.228; 1.G.238.229; 1.G.238.230; 1.G.238.231; 1.G.238.236; 1.G.238.237; 1.G.238.238; 1.G.238.239; 1.G.238.154; 1.G.238.157; 1.G.238.166; 1.G.238.169; 1.G.238.172; 1.G.238.175; 1.G.238.240; 1.G.238.244; 1.G.239.228; 1.G.239.229; 1.G.239.230; 1.G.239.231; 1.G.239.236; 1.G.239.237; 1.G.239.238; 1.G.239.239; 1.G.239.154; 1.G.239.157; 1.G.239.166; 1.G.239.169; 1.G.239.172; 1.G.239.175; 1.G.239.240; 1.G.239.244; 1.G.154.228; 1.G.154.229; 1.G.154.230; 1.G.154.231; 1.G.154.236; 1.G.154.237; 1.G.154.238; 1.G.154.239; 1.G.154.154; 1.G.154.157; 1.G.154.166; 1.G.154.169; 1.G.154.172; 1.G.154.175; 1.G.154.240; 1.G.154.244; 1.G.157.228; 1.G.157.229; 1.G.157.230; 1.G.157.231; 1.G.157.236; 1.G.157.237; 1.G.157.238; 1.G.157.239; 1.G.157.154; 1.G.157.157; 1.G.157.166; 1.G.157.169; 1.G.157.172; 1.G.157.175; 1.G.157.240; 1.G.157.244; 1.G.166.228; 1.G.166.229; 1.G.166.230; 1.G.166.231; 1.G.166.236; 1.G.166.237; 1.G.166.238; 1.G.166.239; 1.G.166.154; 1.G.166.157; 1.G.166.166; 1.G.166.169; 1.G.166.172; 1.G.166.175; 1.G.166.240; 1.G.166.244; 1.G.169.228; 1.G.169.229; 1.G.169.230; 1.G.169.231; 1.G.169.236; 1.G.169.237; 1.G.169.238; 1.G.169.239; 1.G.169.154; 1.G.169.157; 1.G.169.166; 1.G.169.169; 1.G.169.172; 1.G.169.175; 1.G.169.240; 1.G.169.244; 1.G.172.228; 1.G.172.229; 1.G.172.230; 1.G.172.231; 1.G.172.236; 1.G.172.237; 1.G.172.238; 1.G.172.239; 1.G.172.154; 1.G.172.157; 1.G.172.166; 1.G.172.169; 1.G.172.172; 1.G.172.175; 1.G.172.240; 1.G.172.244; 1.G.175.228; 1.G.175.229; 1.G.175.230; 1.G.175.231; 1.G.175.236; 1.G.175.237; 1.G.175.238; 1.G.175.239; 1.G.175.154; 1.G.175.157; 1.G.175.166; 1.G.175.169; 1.G.175.172; 1.G.175.175; 1.G.175.240; 1.G.175.244; 1.G.240.228; 1.G.240.229; 1.G.240.230; 1.G.240.231; 1.G.240.236; 1.G.240.237; 1.G.240.238; 1.G.240.239; 1.G.240.154; 1.G.240.157; 1.G.240.166; 1.G.240.169; 1.G.240.172; 1.G.240.175; 1.G.240.240; 1.G.240.244; 1.G.244.228; 1.G.244.229; 1.G.244.230; 1.G.244.231; 1.G.244.236; 1.G.244.237; 1.G.244.238; 1.G.244.239; 1.G.244.154; 1.G.244.157; 1.G.244.166; 1.G.244.169; 1.G.244.172; 1.G.244.175; 1.G.244.240; 1.G.244.244;

Prodrugs of 1.I

1.I.228.228; 1.I.228.229; 1.I.228.230; 1.I.228.231; 1.I.228.236; 1.I.228.237; 1.I.228.238; 1.I.228.239; 1.I.228.154; 1.I.228.157; 1.I.228.166; 1.I.228.169; 1.I.228.172; 1.I.228.175; 1.I.228.240; 1.I.228.244; 1.I.229.228; 1.I.229.229; 1.I.229.230; 1.I.229.231; 1.I.229.236; 1.I.229.237; 1.I.229.238; 1.I.229.239; 1.I.229.154; 1.I.229.157; 1.I.229.166; 1.I.229.169; 1.I.229.172; 1.I.229.175; 1.I.229.240; 1.I.229.244; 1.I.230.228; 1.I.230.229; 1.I.230.230; 1.I.230.231; 1.I.230.236; 1.I.230.237; 1.I.230.238; 1.I.230.239; 1.I.230.154; 1.I.230.157; 1.I.230.166; 1.I.230.169; 1.I.230.172; 1.I.230.175; 1.I.230.240; 1.I.230.244; 1.I.231.228; 1.I.231.229; 1.I.231.230; 1.I.231.231; 1.I.231.236; 1.I.231.237; 1.I.231.238; 1.I.231.239; 1.I.231.154; 1.I.231.157; 1.I.231.166; 1.I.231.169; 1.I.231.172; 1.I.231.175; 1.I.231.240; 1.I.231.244; 1.I.236.228; 1.I.236.229; 1.I.236.230; 1.I.236.231; 1.I.236.236; 1.I.236.237; 1.I.236.238; 1.I.236.239; 1.I.236.154; 1.I.236.157; 1.I.236.166; 1.I.236.169; 1.I.236.172; 1.I.236.175; 1.I.236.240; 1.I.236.244; 1.I.237.228; 1.I.237.229; 1.I.237.230; 1.I.237.231; 1.I.237.236; 1.I.237.237; 1.I.237.238; 1.I.237.239; 1.I.237.154; 1.I.237.157; 1.I.237.166;

1.I.237.169; 1.I.237.172; 1.I.237.175; 1.I.237.240; 1.I.237.244; 1.I.238.228; 1.I.238.229; 1.I.238.230; 1.I.238.231; 1.I.238.236; 1.I.238.237; 1.I.238.238; 1.I.238.239; 1.I.238.154; 1.I.238.157; 1.I.238.166; 1.I.238.169; 1.I.238.172; 1.I.238.175; 1.I.238.240; 1.I.238.244; 1.I.239.228; 1.I.239.229; 1.I.239.230; 1.I.239.231; 1.I.239.236; 1.I.239.237; 1.I.239.238; 1.I.239.239; 1.I.239.154; 1.I.239.157; 1.I.239.166; 1.I.239.169; 1.I.239.172; 1.I.239.175; 1.I.239.240; 1.I.239.244; 1.I.154.228; 1.I.154.229; 1.I.154.230; 1.I.154.231; 1.I.154.236; 1.I.154.237; 1.I.154.238; 1.I.154.239; 1.I.154.154; 1.I.154.157; 1.I.154.166; 1.I.154.169; 1.I.154.172; 1.I.154.175; 1.I.154.240; 1.I.154.244; 1.I.157.228; 1.I.157.229; 1.I.157.230; 1.I.157.231; 1.I.157.236; 1.I.157.237; 1.I.157.238; 1.I.157.239; 1.I.157.154; 1.I.157.157; 1.I.157.166; 1.I.157.169; 1.I.157.172; 1.I.157.175; 1.I.157.240; 1.I.157.244; 1.I.166.228; 1.I.166.229; 1.I.166.230; 1.I.166.231; 1.I.166.236; 1.I.166.237; 1.I.166.238; 1.I.166.239; 1.I.166.154; 1.I.166.157; 1.I.166.166; 1.I.166.169; 1.I.166.172; 1.I.166.175; 1.I.166.240; 1.I.166.244; 1.I.169.228; 1.I.169.229; 1.I.169.230; 1.I.169.231; 1.I.169.236; 1.I.169.237; 1.I.169.238; 1.I.169.239; 1.I.169.154; 1.I.169.157; 1.I.169.166; 1.I.169.169; 1.I.169.172; 1.I.169.175; 1.I.169.240; 1.I.169.244; 1.I.172.228; 1.I.172.229; 1.I.172.230; 1.I.172.231; 1.I.172.236; 1.I.172.237; 1.I.172.238; 1.I.172.239; 1.I.172.154; 1.I.172.157; 1.I.172.166; 1.I.172.169; 1.I.172.172; 1.I.172.175; 1.I.172.240; 1.I.172.244; 1.I.175.228; 1.I.175.229; 1.I.175.230; 1.I.175.231; 1.I.175.236; 1.I.175.237; 1.I.175.238; 1.I.175.239; 1.I.175.154; 1.I.175.157; 1.I.175.166; 1.I.175.169; 1.I.175.172; 1.I.175.175; 1.I.175.240; 1.I.175.244; 1.I.240.228; 1.I.240.229; 1.I.240.230; 1.I.240.231; 1.I.240.236; 1.I.240.237; 1.I.240.238; 1.I.240.239; 1.I.240.154; 1.I.240.157; 1.I.240.166; 1.I.240.169; 1.I.240.172; 1.I.240.175; 1.I.240.240; 1.I.240.244; 1.I.244.228; 1.I.244.229; 1.I.244.230; 1.I.244.231; 1.I.244.236; 1.I.244.237; 1.I.244.238; 1.I.244.239; 1.I.244.154; 1.I.244.157; 1.I.244.166; 1.I.244.169; 1.I.244.172; 1.I.244.175; 1.I.244.240; 1.I.244.244;

Prodrugs of 1.J

1.J.228.228; 1.J.228.229; 1.J.228.230; 1.J.228.231; 1.J.228.236; 1.J.228.237; 1.J.228.238; 1.J.228.239; 1.J.228.154; 1.J.228.157; 1.J.228.166; 1.J.228.169; 1.J.228.172; 1.J.228.175; 1.J.228.240; 1.J.228.244; 1.J.229.228; 1.J.229.229; 1.J.229.230; 1.J.229.231; 1.J.229.236; 1.J.229.237; 1.J.229.238; 1.J.229.239; 1.J.229.154; 1.J.229.157; 1.J.229.166; 1.J.229.169; 1.J.229.172; 1.J.229.175; 1.J.229.240; 1.J.229.244; 1.J.230.228; 1.J.230.229; 1.J.230.230; 1.J.230.231; 1.J.230.236; 1.J.230.237; 1.J.230.238; 1.J.230.239; 1.J.230.154; 1.J.230.157; 1.J.230.166; 1.J.230.169; 1.J.230.172; 1.J.230.175; 1.J.230.240; 1.J.230.244; 1.J.231.228; 1.J.231.229; 1.J.231.230; 1.J.231.231; 1.J.231.236; 1.J.231.237; 1.J.231.238; 1.J.231.239; 1.J.231.154; 1.J.231.157; 1.J.231.166; 1.J.231.169; 1.J.231.172; 1.J.231.175; 1.J.231.240; 1.J.231.244; 1.J.236.228; 1.J.236.229; 1.J.236.230; 1.J.236.231; 1.J.236.236; 1.J.236.237; 1.J.236.238; 1.J.236.239; 1.J.236.154; 1.J.236.157; 1.J.236.166; 1.J.236.169; 1.J.236.172; 1.J.236.175; 1.J.236.240; 1.J.236.244; 1.J.237.228; 1.J.237.229; 1.J.237.230; 1.J.237.231; 1.J.237.236; 1.J.237.237; 1.J.237.238; 1.J.237.239; 1.J.237.154; 1.J.237.157; 1.J.237.166; 1.J.237.169; 1.J.237.172; 1.J.237.175; 1.J.237.240; 1.J.237.244; 1.J.238.228; 1.J.238.229; 1.J.238.230; 1.J.238.231; 1.J.238.236; 1.J.238.237; 1.J.238.238; 1.J.238.239; 1.J.238.154; 1.J.238.157; 1.J.238.166; 1.J.238.169; 1.J.238.172; 1.J.238.175; 1.J.238.240; 1.J.238.244; 1.J.239.228; 1.J.239.229; 1.J.239.230; 1.J.239.231; 1.J.239.236; 1.J.239.237; 1.J.239.238; 1.J.239.239; 1.J.239.154; 1.J.239.157; 1.J.239.166; 1.J.239.169; 1.J.239.172; 1.J.239.175; 1.J.239.240; 1.J.239.244; 1.J.154.228; 1.J.154.229; 1.J.154.230; 1.J.154.231; 1.J.154.236; 1.J.154.237; 1.J.154.238; 1.J.154.239; 1.J.154.154; 1.J.154.157; 1.J.154.166; 1.J.154.169;

1.J.154.172; 1.J.154.175; 1.J.154.240; 1.J.154.244; 1.J.157.228; 1.J.157.229; 1.J.157.230; 1.J.157.231; 1.J.157.236; 1.J.157.237; 1.J.157.238; 1.J.157.239; 1.J.157.154; 1.J.157.157; 1.J.157.166; 1.J.157.169; 1.J.157.172; 1.J.157.175; 1.J.157.240; 1.J.157.244; 1.J.166.228; 1.J.166.229; 1.J.166.230; 1.J.166.231; 1.J.166.236; 1.J.166.237; 1.J.166.238; 1.J.166.239; 1.J.166.154; 1.J.166.157; 1.J.166.166; 1.J.166.169; 1.J.166.172; 1.J.166.175; 1.J.166.240; 1.J.166.244; 1.J.169.228; 1.J.169.229; 1.J.169.230; 1.J.169.231; 1.J.169.236; 1.J.169.237; 1.J.169.238; 1.J.169.239; 1.J.169.154; 1.J.169.157; 1.J.169.166; 1.J.169.169; 1.J.169.172; 1.J.169.175; 1.J.169.240; 1.J.169.244; 1.J.172.228; 1.J.172.229; 1.J.172.230; 1.J.172.231; 1.J.172.236; 1.J.172.237; 1.J.172.238; 1.J.172.239; 1.J.172.154; 1.J.172.157; 1.J.172.166; 1.J.172.169; 1.J.172.172; 1.J.172.175; 1.J.172.240; 1.J.172.244; 1.J.175.228; 1.J.175.229; 1.J.175.230; 1.J.175.231; 1.J.175.236; 1.J.175.237; 1.J.175.238; 1.J.175.239; 1.J.175.154; 1.J.175.157; 1.J.175.166; 1.J.175.169; 1.J.175.172; 1.J.175.175; 1.J.175.240; 1.J.175.244; 1.J.240.228; 1.J.240.229; 1.J.240.230; 1.J.240.231; 1.J.240.236; 1.J.240.237; 1.J.240.238; 1.J.240.239; 1.J.240.154; 1.J.240.157; 1.J.240.166; 1.J.240.169; 1.J.240.172; 1.J.240.175; 1.J.240.240; 1.J.240.244; 1.J.244.228; 1.J.244.229; 1.J.244.230; 1.J.244.231; 1.J.244.236; 1.J.244.237; 1.J.244.238; 1.J.244.239; 1.J.244.154; 1.J.244.157; 1.J.244.166; 1.J.244.169; 1.J.244.172; 1.J.244.175; 1.J.244.240; 1.J.244.244;

Prodrugs of 1.L

1.L.228.228; 1.L.228.229; 1.L.228.230; 1.L.228.231; 1.L.228.236; 1.L.228.237; 1.L.228.238; 1.L.228.239; 1.L.228.154; 1.L.228.157; 1.L.228.166; 1.L.228.169; 1.L.228.172; 1.L.228.175; 1.L.228.240; 1.L.228.244; 1.L.229.228; 1.L.229.229; 1.L.229.230; 1.L.229.231; 1.L.229.236; 1.L.229.237; 1.L.229.238; 1.L.229.239; 1.L.229.154; 1.L.229.157; 1.L.229.166; 1.L.229.169; 1.L.229.172; 1.L.229.175; 1.L.229.240; 1.L.229.244; 1.L.230.228; 1.L.230.229; 1.L.230.230; 1.L.230.231; 1.L.230.236; 1.L.230.237; 1.L.230.238; 1.L.230.239; 1.L.230.154; 1.L.230.157; 1.L.230.166; 1.L.230.169; 1.L.230.172; 1.L.230.175; 1.L.230.240; 1.L.230.244; 1.L.231.228; 1.L.231.229; 1.L.231.230; 1.L.231.231; 1.L.231.236; 1.L.231.237; 1.L.231.238; 1.L.231.239; 1.L.231.154; 1.L.231.157; 1.L.231.166; 1.L.231.169; 1.L.231.172; 1.L.231.175; 1.L.231.240; 1.L.231.244; 1.L.236.228; 1.L.236.229; 1.L.236.230; 1.L.236.231; 1.L.236.236; 1.L.236.237; 1.L.236.238; 1.L.236.239; 1.L.236.154; 1.L.236.157; 1.L.236.166; 1.L.236.169; 1.L.236.172; 1.L.236.175; 1.L.236.240; 1.L.236.244; 1.L.237.228; 1.L.237.229; 1.L.237.230; 1.L.237.231; 1.L.237.236; 1.L.237.237; 1.L.237.238; 1.L.237.239; 1.L.237.154; 1.L.237.157; 1.L.237.166; 1.L.237.169; 1.L.237.172; 1.L.237.175; 1.L.237.240; 1.L.237.244; 1.L.238.228; 1.L.238.229; 1.L.238.230; 1.L.238.231; 1.L.238.236; 1.L.238.237; 1.L.238.238; 1.L.238.239; 1.L.238.154; 1.L.238.157; 1.L.238.166; 1.L.238.169; 1.L.238.172; 1.L.238.175; 1.L.238.240; 1.L.238.244; 1.L.239.228; 1.L.239.229; 1.L.239.230; 1.L.239.231; 1.L.239.236; 1.L.239.237; 1.L.239.238; 1.L.239.239; 1.L.239.154; 1.L.239.157; 1.L.239.166; 1.L.239.169; 1.L.239.172; 1.L.239.175; 1.L.239.240; 1.L.239.244; 1.L.154.228; 1.L.154.229; 1.L.154.230; 1.L.154.231; 1.L.154.236; 1.L.154.237; 1.L.154.238; 1.L.154.239; 1.L.154.154; 1.L.154.157; 1.L.154.166; 1.L.154.169; 1.L.154.172; 1.L.154.175; 1.L.154.240; 1.L.154.244; 1.L.157.228; 1.L.157.229; 1.L.157.230; 1.L.157.231; 1.L.157.236; 1.L.157.237; 1.L.157.238; 1.L.157.239; 1.L.157.154; 1.L.157.157; 1.L.157.166; 1.L.157.169; 1.L.157.172; 1.L.157.175; 1.L.157.240; 1.L.157.244; 1.L.166.228; 1.L.166.229; 1.L.166.230; 1.L.166.231; 1.L.166.236; 1.L.166.237; 1.L.166.238; 1.L.166.239; 1.L.166.154; 1.L.166.157; 1.L.166.166; 1.L.166.169; 1.L.166.172; 1.L.166.175; 1.L.166.240; 1.L.166.244; 1.L.169.228; 1.L.169.229; 1.L.169.230; 1.L.169.231; 1.L.169.236; 1.L.169.237; 1.L.169.238; 1.L.169.239; 1.L.169.154; 1.L.169.157; 1.L.169.166; 1.L.169.169;

1.L.169.172; 1.L.169.175; 1.L.169.240; 1.L.169.244; 1.L.172.228; 1.L.172.229; 1.L.172.230; 1.L.172.231; 1.L.172.236; 1.L.172.237; 1.L.172.238; 1.L.172.239; 1.L.172.154; 1.L.172.157; 1.L.172.166; 1.L.172.169; 1.L.172.172; 1.L.172.175; 1.L.172.240; 1.L.172.244; 1.L.175.228; 1.L.175.229; 1.L.175.230; 1.L.175.231; 1.L.175.236; 1.L.175.237; 1.L.175.238; 1.L.175.239; 1.L.175.154; 1.L.175.157; 1.L.175.166; 1.L.175.169; 1.L.175.172; 1.L.175.175; 1.L.175.240; 1.L.175.244; 1.L.240.228; 1.L.240.229; 1.L.240.230; 1.L.240.231; 1.L.240.236; 1.L.240.237; 1.L.240.238; 1.L.240.239; 1.L.240.154; 1.L.240.157; 1.L.240.166; 1.L.240.169; 1.L.240.172; 1.L.240.175; 1.L.240.240; 1.L.240.244; 1.L.244.228; 1.L.244.229; 1.L.244.230; 1.L.244.231; 1.L.244.236; 1.L.244.237; 1.L.244.238; 1.L.244.239; 1.L.244.154; 1.L.244.157; 1.L.244.166; 1.L.244.169; 1.L.244.172; 1.L.244.175; 1.L.244.240; 1.L.244.244;

Prodrugs of 1.O

1.O.228.228; 1.O.228.229; 1.O.228.230; 1.O.228.231; 1.O.228.236; 1.O.228.237; 1.O.228.238; 1.O.228.239; 1.O.228.154; 1.O.228.157; 1.O.228.166; 1.O.228.169; 1.O.228.172; 1.O.228.175; 1.O.228.240; 1.O.228.244; 1.O.229.228; 1.O.229.229; 1.O.229.230; 1.O.229.231; 1.O.229.236; 1.O.229.237; 1.O.229.238; 1.O.229.239; 1.O.229.154; 1.O.229.157; 1.O.229.166; 1.O.229.169; 1.O.229.172; 1.O.229.175; 1.O.229.240; 1.O.229.244; 1.O.230.228; 1.O.230.229; 1.O.230.230; 1.O.230.231; 1.O.230.236; 1.O.230.237; 1.O.230.238; 1.O.230.239; 1.O.230.154; 1.O.230.157; 1.O.230.166; 1.O.230.169; 1.O.230.172; 1.O.230.175; 1.O.230.240; 1.O.230.244; 1.O.231.228; 1.O.231.229; 1.O.231.230; 1.O.231.231; 1.O.231.236; 1.O.231.237; 1.O.231.238; 1.O.231.239; 1.O.231.154; 1.O.231.157; 1.O.231.166; 1.O.231.169; 1.O.231.172; 1.O.231.175; 1.O.231.240; 1.O.231.244; 1.O.236.228; 1.O.236.229; 1.O.236.230; 1.O.236.231; 1.O.236.236; 1.O.236.237; 1.O.236.238; 1.O.236.239; 1.O.236.154; 1.O.236.157; 1.O.236.166; 1.O.236.169; 1.O.236.172; 1.O.236.175; 1.O.236.240; 1.O.236.244; 1.O.237.228; 1.O.237.229; 1.O.237.230; 1.O.237.231; 1.O.237.236; 1.O.237.237; 1.O.237.238; 1.O.237.239; 1.O.237.154; 1.O.237.157; 1.O.237.166; 1.O.237.169; 1.O.237.172; 1.O.237.175; 1.O.237.240; 1.O.237.244; 1.O.238.228; 1.O.238.229; 1.O.238.230; 1.O.238.231; 1.O.238.236; 1.O.238.237; 1.O.238.238; 1.O.238.239; 1.O.238.154; 1.O.238.157; 1.O.238.166; 1.O.238.169; 1.O.238.172; 1.O.238.175; 1.O.238.240; 1.O.238.244; 1.O.239.228; 1.O.239.229; 1.O.239.230; 1.O.239.231; 1.O.239.236; 1.O.239.237; 1.O.239.238; 1.O.239.239; 1.O.239.154; 1.O.239.157; 1.O.239.166; 1.O.239.169; 1.O.239.172; 1.O.239.175; 1.O.239.240; 1.O.239.244; 1.O.154.228; 1.O.154.229; 1.O.154.230; 1.O.154.231; 1.O.154.236; 1.O.154.237; 1.O.154.238; 1.O.154.239; 1.O.154.154; 1.O.154.157; 1.O.154.166; 1.O.154.169; 1.O.154.172; 1.O.154.175; 1.O.154.240; 1.O.154.244; 1.O.157.228; 1.O.157.229; 1.O.157.230; 1.O.157.231; 1.O.157.236; 1.O.157.237; 1.O.157.238; 1.O.157.239; 1.O.157.154; 1.O.157.157; 1.O.157.166; 1.O.157.169; 1.O.157.172; 1.O.157.175; 1.O.157.240; 1.O.157.244; 1.O.166.228; 1.O.166.229; 1.O.166.230; 1.O.166.231; 1.O.166.236; 1.O.166.237; 1.O.166.238; 1.O.166.239; 1.O.166.154; 1.O.166.157; 1.O.166.166; 1.O.166.169; 1.O.166.172; 1.O.166.175; 1.O.166.240; 1.O.166.244; 1.O.169.228; 1.O.169.229; 1.O.169.230; 1.O.169.231; 1.O.169.236; 1.O.169.237; 1.O.169.238; 1.O.169.239; 1.O.169.154; 1.O.169.157; 1.O.169.166; 1.O.169.169; 1.O.169.172; 1.O.169.175; 1.O.169.240; 1.O.169.244; 1.O.172.228; 1.O.172.229; 1.O.172.230; 1.O.172.231; 1.O.172.236; 1.O.172.237; 1.O.172.238; 1.O.172.239; 1.O.172.154; 1.O.172.157; 1.O.172.166; 1.O.172.169;

1.O.172.172; 1.O.172.175; 1.O.172.240; 1.O.172.244; 1.O.175.228; 1.O.175.229; 1.O.175.230; 1.O.175.231; 1.O.175.236; 1.O.175.237; 1.O.175.238; 1.O.175.239; 1.O.175.154; 1.O.175.157; 1.O.175.166; 1.O.175.169; 1.O.175.172; 1.O.175.175; 1.O.175.240; 1.O.175.244; 1.O.240.228; 1.O.240.229; 1.O.240.230; 1.O.240.231; 1.O.240.236; 1.O.240.237; 1.O.240.238; 1.O.240.239; 1.O.240.154; 1.O.240.157; 1.O.240.166; 1.O.240.169; 1.O.240.172; 1.O.240.175; 1.O.240.240; 1.O.240.244; 1.O.244.228; 1.O.244.229; 1.O.244.230; 1.O.244.231; 1.O.244.236; 1.O.244.237; 1.O.244.238; 1.O.244.239; 1.O.244.154; 1.O.244.157; 1.O.244.166; 1.O.244.169; 1.O.244.172; 1.O.244.175; 1.O.244.240; 1.O.244.244;

<u>Prodrugs of 1.P</u>

1.P.228.228; 1.P.228.229; 1.P.228.230; 1.P.228.231; 1.P.228.236; 1.P.228.237; 1.P.228.238; 1.P.228.239; 1.P.228.154; 1.P.228.157; 1.P.228.166; 1.P.228.169; 1.P.228.172; 1.P.228.175; 1.P.228.240; 1.P.228.244; 1.P.229.228; 1.P.229.229; 1.P.229.230; 1.P.229.231; 1.P.229.236; 1.P.229.237; 1.P.229.238; 1.P.229.239; 1.P.229.154; 1.P.229.157; 1.P.229.166; 1.P.229.169; 1.P.229.172; 1.P.229.175; 1.P.229.240; 1.P.229.244; 1.P.230.228; 1.P.230.229; 1.P.230.230; 1.P.230.231; 1.P.230.236; 1.P.230.237; 1.P.230.238; 1.P.230.239; 1.P.230.154; 1.P.230.157; 1.P.230.166; 1.P.230.169; 1.P.230.172; 1.P.230.175; 1.P.230.240; 1.P.230.244; 1.P.231.228; 1.P.231.229; 1.P.231.230; 1.P.231.231; 1.P.231.236; 1.P.231.237; 1.P.231.238; 1.P.231.239; 1.P.231.154; 1.P.231.157; 1.P.231.166; 1.P.231.169; 1.P.231.172; 1.P.231.175; 1.P.231.240; 1.P.231.244; 1.P.236.228; 1.P.236.229; 1.P.236.230; 1.P.236.231; 1.P.236.236; 1.P.236.237; 1.P.236.238; 1.P.236.239; 1.P.236.154; 1.P.236.157; 1.P.236.166; 1.P.236.169; 1.P.236.172; 1.P.236.175; 1.P.236.240; 1.P.236.244; 1.P.237.228; 1.P.237.229; 1.P.237.230; 1.P.237.231; 1.P.237.236; 1.P.237.237; 1.P.237.238; 1.P.237.239; 1.P.237.154; 1.P.237.157; 1.P.237.166; 1.P.237.169; 1.P.237.172; 1.P.237.175; 1.P.237.240; 1.P.237.244; 1.P.238.228; 1.P.238.229; 1.P.238.230; 1.P.238.231; 1.P.238.236; 1.P.238.237; 1.P.238.238; 1.P.238.239; 1.P.238.154; 1.P.238.157; 1.P.238.166; 1.P.238.169; 1.P.238.172; 1.P.238.175; 1.P.238.240; 1.P.238.244; 1.P.239.228; 1.P.239.229; 1.P.239.230; 1.P.239.231; 1.P.239.236; 1.P.239.237; 1.P.239.238; 1.P.239.239; 1.P.239.154; 1.P.239.157; 1.P.239.166; 1.P.239.169; 1.P.239.172; 1.P.239.175; 1.P.239.240; 1.P.239.244; 1.P.154.228; 1.P.154.229; 1.P.154.230; 1.P.154.231; 1.P.154.236; 1.P.154.237; 1.P.154.238; 1.P.154.239; 1.P.154.154; 1.P.154.157; 1.P.154.166; 1.P.154.169; 1.P.154.172; 1.P.154.175; 1.P.154.240; 1.P.154.244; 1.P.157.228; 1.P.157.229; 1.P.157.230; 1.P.157.231; 1.P.157.236; 1.P.157.237; 1.P.157.238; 1.P.157.239; 1.P.157.154; 1.P.157.157; 1.P.157.166; 1.P.157.169; 1.P.157.172; 1.P.157.175; 1.P.157.240; 1.P.157.244; 1.P.166.228; 1.P.166.229; 1.P.166.230; 1.P.166.231; 1.P.166.236; 1.P.166.237; 1.P.166.238; 1.P.166.239; 1.P.166.154; 1.P.166.157; 1.P.166.166; 1.P.166.169; 1.P.166.172; 1.P.166.175; 1.P.166.240; 1.P.166.244; 1.P.169.228; 1.P.169.229; 1.P.169.230; 1.P.169.231; 1.P.169.236; 1.P.169.237; 1.P.169.238; 1.P.169.239; 1.P.169.154; 1.P.169.157; 1.P.169.166; 1.P.169.169; 1.P.169.172; 1.P.169.175; 1.P.169.240; 1.P.169.244; 1.P.172.228; 1.P.172.229; 1.P.172.230; 1.P.172.231; 1.P.172.236; 1.P.172.237; 1.P.172.238; 1.P.172.239; 1.P.172.154; 1.P.172.157; 1.P.172.166; 1.P.172.169; 1.P.172.172; 1.P.172.175; 1.P.172.240; 1.P.172.244; 1.P.175.228; 1.P.175.229; 1.P.175.230; 1.P.175.231; 1.P.175.236; 1.P.175.237; 1.P.175.238; 1.P.175.239; 1.P.175.154; 1.P.175.157; 1.P.175.166; 1.P.175.169; 1.P.175.172; 1.P.175.175; 1.P.175.240; 1.P.175.244; 1.P.240.228; 1.P.240.229; 1.P.240.230; 1.P.240.231; 1.P.240.236; 1.P.240.237; 1.P.240.238; 1.P.240.239; 1.P.240.154; 1.P.240.157; 1.P.240.166; 1.P.240.169; 1.P.240.172; 1.P.240.175; 1.P.240.240; 1.P.240.244; 1.P.244.228; 1.P.244.229; 1.P.244.230; 1.P.244.231;

1.P.244.236; 1.P.244.237; 1.P.244.238; 1.P.244.239; 1.P.244.154; 1.P.244.157; 1.P.244.166; 1.P.244.169; 1.P.244.172; 1.P.244.175; 1.P.244.240; 1.P.244.244;

Prodrugs of 1.U

1.U.228.228; 1.U.228.229; 1.U.228.230; 1.U.228.231; 1.U.228.236; 1.U.228.237; 1.U.228.238; 1.U.228.239; 1.U.228.154; 1.U.228.157; 1.U.228.166; 1.U.228.169; 1.U.228.172; 1.U.228.175; 1.U.228.240; 1.U.228.244; 1.U.229.228; 1.U.229.229; 1.U.229.230; 1.U.229.231; 1.U.229.236; 1.U.229.237; 1.U.229.238; 1.U.229.239; 1.U.229.154; 1.U.229.157; 1.U.229.166; 1.U.229.169; 1.U.229.172; 1.U.229.175; 1.U.229.240; 1.U.229.244; 1.U.230.228; 1.U.230.229; 1.U.230.230; 1.U.230.231; 1.U.230.236; 1.U.230.237; 1.U.230.238; 1.U.230.239; 1.U.230.154; 1.U.230.157; 1.U.230.166; 1.U.230.169; 1.U.230.172; 1.U.230.175; 1.U.230.240; 1.U.230.244; 1.U.231.228; 1.U.231.229; 1.U.231.230; 1.U.231.231; 1.U.231.236; 1.U.231.237; 1.U.231.238; 1.U.231.239; 1.U.231.154; 1.U.231.157; 1.U.231.166; 1.U.231.169; 1.U.231.172; 1.U.231.175; 1.U.231.240; 1.U.231.244; 1.U.236.228; 1.U.236.229; 1.U.236.230; 1.U.236.231; 1.U.236.236; 1.U.236.237; 1.U.236.238; 1.U.236.239; 1.U.236.154; 1.U.236.157; 1.U.236.166; 1.U.236.169; 1.U.236.172; 1.U.236.175; 1.U.236.240; 1.U.236.244; 1.U.237.228; 1.U.237.229; 1.U.237.230; 1.U.237.231; 1.U.237.236; 1.U.237.237; 1.U.237.238; 1.U.237.239; 1.U.237.154; 1.U.237.157; 1.U.237.166; 1.U.237.169; 1.U.237.172; 1.U.237.175; 1.U.237.240; 1.U.237.244; 1.U.238.228; 1.U.238.229; 1.U.238.230; 1.U.238.231; 1.U.238.236; 1.U.238.237; 1.U.238.238; 1.U.238.239; 1.U.238.154; 1.U.238.157; 1.U.238.166; 1.U.238.169; 1.U.238.172; 1.U.238.175; 1.U.238.240; 1.U.238.244; 1.U.239.228; 1.U.239.229; 1.U.239.230; 1.U.239.231; 1.U.239.236; 1.U.239.237; 1.U.239.238; 1.U.239.239; 1.U.239.154; 1.U.239.157; 1.U.239.166; 1.U.239.169; 1.U.239.172; 1.U.239.175; 1.U.239.240; 1.U.239.244; 1.U.154.228; 1.U.154.229; 1.U.154.230; 1.U.154.231; 1.U.154.236; 1.U.154.237; 1.U.154.238; 1.U.154.239; 1.U.154.154; 1.U.154.157; 1.U.154.166; 1.U.154.169; 1.U.154.172; 1.U.154.175; 1.U.154.240; 1.U.154.244; 1.U.157.228; 1.U.157.229; 1.U.157.230; 1.U.157.231; 1.U.157.236; 1.U.157.237; 1.U.157.238; 1.U.157.239; 1.U.157.154; 1.U.157.157; 1.U.157.166; 1.U.157.169; 1.U.157.172; 1.U.157.175; 1.U.157.240; 1.U.157.244; 1.U.166.228; 1.U.166.229; 1.U.166.230; 1.U.166.231; 1.U.166.236; 1.U.166.237; 1.U.166.238; 1.U.166.239; 1.U.166.154; 1.U.166.157; 1.U.166.166; 1.U.166.169; 1.U.166.172; 1.U.166.175; 1.U.166.240; 1.U.166.244; 1.U.169.228; 1.U.169.229; 1.U.169.230; 1.U.169.231; 1.U.169.236; 1.U.169.237; 1.U.169.238; 1.U.169.239; 1.U.169.154; 1.U.169.157; 1.U.169.166; 1.U.169.169; 1.U.169.172; 1.U.169.175; 1.U.169.240; 1.U.169.244; 1.U.172.228; 1.U.172.229; 1.U.172.230; 1.U.172.231; 1.U.172.236; 1.U.172.237; 1.U.172.238; 1.U.172.239; 1.U.172.154; 1.U.172.157; 1.U.172.166; 1.U.172.169; 1.U.172.172; 1.U.172.175; 1.U.172.240; 1.U.172.244; 1.U.175.228; 1.U.175.229; 1.U.175.230; 1.U.175.231; 1.U.175.236; 1.U.175.237; 1.U.175.238; 1.U.175.239; 1.U.175.154; 1.U.175.157; 1.U.175.166; 1.U.175.169; 1.U.175.172; 1.U.175.175; 1.U.175.240; 1.U.175.244; 1.U.240.228; 1.U.240.229; 1.U.240.230; 1.U.240.231; 1.U.240.236; 1.U.240.237; 1.U.240.238; 1.U.240.239; 1.U.240.154; 1.U.240.157; 1.U.240.166; 1.U.240.169; 1.U.240.172; 1.U.240.175; 1.U.240.240; 1.U.240.244; 1.U.244.228; 1.U.244.229; 1.U.244.230; 1.U.244.231; 1.U.244.236; 1.U.244.237;

1.U.244.238; 1.U.244.239; 1.U.244.154; 1.U.244.157; 1.U.244.166; 1.U.244.169; 1.U.244.172; 1.U.244.175; 1.U.244.240; 1.U.244.244;

<u>Prodrugs of 1.W</u>

1.W.228.228; 1.W.228.229; 1.W.228.230; 1.W.228.231; 1.W.228.236; 1.W.228.237; 1.W.228.238; 1.W.228.239; 1.W.228.154; 1.W.228.157; 1.W.228.166; 1.W.228.169; 1.W.228.172; 1.W.228.175; 1.W.228.240; 1.W.228.244; 1.W.229.228; 1.W.229.229; 1.W.229.230; 1.W.229.231; 1.W.229.236; 1.W.229.237; 1.W.229.238; 1.W.229.239; 1.W.229.154; 1.W.229.157; 1.W.229.166; 1.W.229.169; 1.W.229.172; 1.W.229.175; 1.W.229.240; 1.W.229.244; 1.W.230.228; 1.W.230.229; 1.W.230.230; 1.W.230.231; 1.W.230.236; 1.W.230.237; 1.W.230.238; 1.W.230.239; 1.W.230.154; 1.W.230.157; 1.W.230.166; 1.W.230.169; 1.W.230.172; 1.W.230.175; 1.W.230.240; 1.W.230.244; 1.W.231.228; 1.W.231.229; 1.W.231.230; 1.W.231.231; 1.W.231.236; 1.W.231.237; 1.W.231.238; 1.W.231.239; 1.W.231.154; 1.W.231.157; 1.W.231.166; 1.W.231.169; 1.W.231.172; 1.W.231.175; 1.W.231.240; 1.W.231.244; 1.W.236.228; 1.W.236.229; 1.W.236.230; 1.W.236.231; 1.W.236.236; 1.W.236.237; 1.W.236.238; 1.W.236.239; 1.W.236.154; 1.W.236.157; 1.W.236.166; 1.W.236.169; 1.W.236.172; 1.W.236.175; 1.W.236.240; 1.W.236.244; 1.W.237.228; 1.W.237.229; 1.W.237.230; 1.W.237.231; 1.W.237.236; 1.W.237.237; 1.W.237.238; 1.W.237.239; 1.W.237.154; 1.W.237.157; 1.W.237.166; 1.W.237.169; 1.W.237.172; 1.W.237.175; 1.W.237.240; 1.W.237.244; 1.W.238.228; 1.W.238.229; 1.W.238.230; 1.W.238.231; 1.W.238.236; 1.W.238.237; 1.W.238.238; 1.W.238.239; 1.W.238.154; 1.W.238.157; 1.W.238.166; 1.W.238.169; 1.W.238.172; 1.W.238.175; 1.W.238.240; 1.W.238.244; 1.W.239.228; 1.W.239.229; 1.W.239.230; 1.W.239.231; 1.W.239.236; 1.W.239.237; 1.W.239.238; 1.W.239.239; 1.W.239.154; 1.W.239.157; 1.W.239.166; 1.W.239.169; 1.W.239.172; 1.W.239.175; 1.W.239.240; 1.W.239.244; 1.W.154.228; 1.W.154.229; 1.W.154.230; 1.W.154.231; 1.W.154.236; 1.W.154.237; 1.W.154.238; 1.W.154.239; 1.W.154.154; 1.W.154.157; 1.W.154.166; 1.W.154.169; 1.W.154.172; 1.W.154.175; 1.W.154.240; 1.W.154.244; 1.W.157.228; 1.W.157.229; 1.W.157.230; 1.W.157.231; 1.W.157.236; 1.W.157.237; 1.W.157.238; 1.W.157.239; 1.W.157.154; 1.W.157.157; 1.W.157.166; 1.W.157.169; 1.W.157.172; 1.W.157.175; 1.W.157.240; 1.W.157.244; 1.W.166.228; 1.W.166.229; 1.W.166.230; 1.W.166.231; 1.W.166.236; 1.W.166.237; 1.W.166.238; 1.W.166.239; 1.W.166.154; 1.W.166.157; 1.W.166.166; 1.W.166.169; 1.W.166.172; 1.W.166.175; 1.W.166.240; 1.W.166.244; 1.W.169.228; 1.W.169.229; 1.W.169.230; 1.W.169.231; 1.W.169.236; 1.W.169.237; 1.W.169.238; 1.W.169.239; 1.W.169.154; 1.W.169.157; 1.W.169.166; 1.W.169.169; 1.W.169.172; 1.W.169.175; 1.W.169.240; 1.W.169.244; 1.W.172.228; 1.W.172.229; 1.W.172.230; 1.W.172.231; 1.W.172.236; 1.W.172.237; 1.W.172.238; 1.W.172.239; 1.W.172.154; 1.W.172.157; 1.W.172.166; 1.W.172.169; 1.W.172.172; 1.W.172.175; 1.W.172.240; 1.W.172.244; 1.W.175.228; 1.W.175.229; 1.W.175.230; 1.W.175.231; 1.W.175.236; 1.W.175.237; 1.W.175.238; 1.W.175.239; 1.W.175.154; 1.W.175.157; 1.W.175.166; 1.W.175.169; 1.W.175.172; 1.W.175.175; 1.W.175.240; 1.W.175.244; 1.W.240.228; 1.W.240.229; 1.W.240.230; 1.W.240.231; 1.W.240.236; 1.W.240.237; 1.W.240.238; 1.W.240.239; 1.W.240.154; 1.W.240.157; 1.W.240.166; 1.W.240.169; 1.W.240.172; 1.W.240.175; 1.W.240.240; 1.W.240.244; 1.W.244.228; 1.W.244.229; 1.W.244.230; 1.W.244.231; 1.W.244.236; 1.W.244.237;

1.W.244.238; 1.W.244.239; 1.W.244.154; 1.W.244.157; 1.W.244.166; 1.W.244.169; 1.W.244.172; 1.W.244.175; 1.W.244.240; 1.W.244.244;

Prodrugs of 1.Y

1.Y.228.228; 1.Y.228.229; 1.Y.228.230; 1.Y.228.231; 1.Y.228.236; 1.Y.228.237; 1.Y.228.238; 1.Y.228.239; 1.Y.228.154; 1.Y.228.157; 1.Y.228.166; 1.Y.228.169; 1.Y.228.172; 1.Y.228.175; 1.Y.228.240; 1.Y.228.244; 1.Y.229.228; 1.Y.229.229; 1.Y.229.230; 1.Y.229.231; 1.Y.229.236; 1.Y.229.237; 1.Y.229.238; 1.Y.229.239; 1.Y.229.154; 1.Y.229.157; 1.Y.229.166; 1.Y.229.169; 1.Y.229.172; 1.Y.229.175; 1.Y.229.240; 1.Y.229.244; 1.Y.230.228; 1.Y.230.229; 1.Y.230.230; 1.Y.230.231; 1.Y.230.236; 1.Y.230.237; 1.Y.230.238; 1.Y.230.239; 1.Y.230.154; 1.Y.230.157; 1.Y.230.166; 1.Y.230.169; 1.Y.230.172; 1.Y.230.175; 1.Y.230.240; 1.Y.230.244; 1.Y.231.228; 1.Y.231.229; 1.Y.231.230; 1.Y.231.231; 1.Y.231.236; 1.Y.231.237; 1.Y.231.238; 1.Y.231.239; 1.Y.231.154; 1.Y.231.157; 1.Y.231.166; 1.Y.231.169; 1.Y.231.172; 1.Y.231.175; 1.Y.231.240; 1.Y.231.244; 1.Y.236.228; 1.Y.236.229; 1.Y.236.230; 1.Y.236.231; 1.Y.236.236; 1.Y.236.237; 1.Y.236.238; 1.Y.236.239; 1.Y.236.154; 1.Y.236.157; 1.Y.236.166; 1.Y.236.169; 1.Y.236.172; 1.Y.236.175; 1.Y.236.240; 1.Y.236.244; 1.Y.237.228; 1.Y.237.229; 1.Y.237.230; 1.Y.237.231; 1.Y.237.236; 1.Y.237.237; 1.Y.237.238; 1.Y.237.239; 1.Y.237.154; 1.Y.237.157; 1.Y.237.166; 1.Y.237.169; 1.Y.237.172; 1.Y.237.175; 1.Y.237.240; 1.Y.237.244; 1.Y.238.228; 1.Y.238.229; 1.Y.238.230; 1.Y.238.231; 1.Y.238.236; 1.Y.238.237; 1.Y.238.238; 1.Y.238.239; 1.Y.238.154; 1.Y.238.157; 1.Y.238.166; 1.Y.238.169; 1.Y.238.172; 1.Y.238.175; 1.Y.238.240; 1.Y.238.244; 1.Y.239.228; 1.Y.239.229; 1.Y.239.230; 1.Y.239.231; 1.Y.239.236; 1.Y.239.237; 1.Y.239.238; 1.Y.239.239; 1.Y.239.154; 1.Y.239.157; 1.Y.239.166; 1.Y.239.169; 1.Y.239.172; 1.Y.239.175; 1.Y.239.240; 1.Y.239.244; 1.Y.154.228; 1.Y.154.229; 1.Y.154.230; 1.Y.154.231; 1.Y.154.236; 1.Y.154.237; 1.Y.154.238; 1.Y.154.239; 1.Y.154.154; 1.Y.154.157; 1.Y.154.166; 1.Y.154.169; 1.Y.154.172; 1.Y.154.175; 1.Y.154.240; 1.Y.154.244; 1.Y.157.228; 1.Y.157.229; 1.Y.157.230; 1.Y.157.231; 1.Y.157.236; 1.Y.157.237; 1.Y.157.238; 1.Y.157.239; 1.Y.157.154; 1.Y.157.157; 1.Y.157.166; 1.Y.157.169; 1.Y.157.172; 1.Y.157.175; 1.Y.157.240; 1.Y.157.244; 1.Y.166.228; 1.Y.166.229; 1.Y.166.230; 1.Y.166.231; 1.Y.166.236; 1.Y.166.237; 1.Y.166.238; 1.Y.166.239; 1.Y.166.154; 1.Y.166.157; 1.Y.166.166; 1.Y.166.169; 1.Y.166.172; 1.Y.166.175; 1.Y.166.240; 1.Y.166.244; 1.Y.169.228; 1.Y.169.229; 1.Y.169.230; 1.Y.169.231; 1.Y.169.236; 1.Y.169.237; 1.Y.169.238; 1.Y.169.239; 1.Y.169.154; 1.Y.169.157; 1.Y.169.166; 1.Y.169.169; 1.Y.169.172; 1.Y.169.175; 1.Y.169.240; 1.Y.169.244; 1.Y.172.228; 1.Y.172.229; 1.Y.172.230; 1.Y.172.231; 1.Y.172.236; 1.Y.172.237; 1.Y.172.238; 1.Y.172.239; 1.Y.172.154; 1.Y.172.157; 1.Y.172.166; 1.Y.172.169; 1.Y.172.172; 1.Y.172.175; 1.Y.172.240; 1.Y.172.244; 1.Y.175.228; 1.Y.175.229; 1.Y.175.230; 1.Y.175.231; 1.Y.175.236; 1.Y.175.237; 1.Y.175.238; 1.Y.175.239; 1.Y.175.154; 1.Y.175.157; 1.Y.175.166; 1.Y.175.169; 1.Y.175.172; 1.Y.175.175; 1.Y.175.240; 1.Y.175.244; 1.Y.240.228; 1.Y.240.229; 1.Y.240.230; 1.Y.240.231; 1.Y.240.236; 1.Y.240.237; 1.Y.240.238; 1.Y.240.239; 1.Y.240.154; 1.Y.240.157; 1.Y.240.166; 1.Y.240.169; 1.Y.240.172; 1.Y.240.175; 1.Y.240.240; 1.Y.240.244; 1.Y.244.228; 1.Y.244.229; 1.Y.244.230; 1.Y.244.231; 1.Y.244.236; 1.Y.244.237;

1.Y.244.238; 1.Y.244.239; 1.Y.244.154; 1.Y.244.157; 1.Y.244.166; 1.Y.244.169; 1.Y.244.172; 1.Y.244.175; 1.Y.244.240; 1.Y.244.244;

Prodrugs of 2.B

2.B.228.228; 2.B.228.229; 2.B.228.230; 2.B.228.231; 2.B.228.236; 2.B.228.237; 2.B.228.238; 2.B.228.239; 2.B.228.154; 2.B.228.157; 2.B.228.166; 2.B.228.169; 2.B.228.172; 2.B.228.175; 2.B.228.240; 2.B.228.244; 2.B.229.228; 2.B.229.229; 2.B.229.230; 2.B.229.231; 2.B.229.236; 2.B.229.237; 2.B.229.238; 2.B.229.239; 2.B.229.154; 2.B.229.157; 2.B.229.166; 2.B.229.169; 2.B.229.172; 2.B.229.175; 2.B.229.240; 2.B.229.244; 2.B.230.228; 2.B.230.229; 2.B.230.230; 2.B.230.231; 2.B.230.236; 2.B.230.237; 2.B.230.238; 2.B.230.239; 2.B.230.154; 2.B.230.157; 2.B.230.166; 2.B.230.169; 2.B.230.172; 2.B.230.175; 2.B.230.240; 2.B.230.244; 2.B.231.228; 2.B.231.229; 2.B.231.230; 2.B.231.231; 2.B.231.236; 2.B.231.237; 2.B.231.238; 2.B.231.239; 2.B.231.154; 2.B.231.157; 2.B.231.166; 2.B.231.169; 2.B.231.172; 2.B.231.175; 2.B.231.240; 2.B.231.244; 2.B.236.228; 2.B.236.229; 2.B.236.230; 2.B.236.231; 2.B.236.236; 2.B.236.237; 2.B.236.238; 2.B.236.239; 2.B.236.154; 2.B.236.157; 2.B.236.166; 2.B.236.169; 2.B.236.172; 2.B.236.175; 2.B.236.240; 2.B.236.244; 2.B.237.228; 2.B.237.229; 2.B.237.230; 2.B.237.231; 2.B.237.236; 2.B.237.237; 2.B.237.238; 2.B.237.239; 2.B.237.154; 2.B.237.157; 2.B.237.166; 2.B.237.169; 2.B.237.172; 2.B.237.175; 2.B.237.240; 2.B.237.244; 2.B.238.228; 2.B.238.229; 2.B.238.230; 2.B.238.231; 2.B.238.236; 2.B.238.237; 2.B.238.238; 2.B.238.239; 2.B.238.154; 2.B.238.157; 2.B.238.166; 2.B.238.169; 2.B.238.172; 2.B.238.175; 2.B.238.240; 2.B.238.244; 2.B.239.228; 2.B.239.229; 2.B.239.230; 2.B.239.231; 2.B.239.236; 2.B.239.237; 2.B.239.238; 2.B.239.239; 2.B.239.154; 2.B.239.157; 2.B.239.166; 2.B.239.169; 2.B.239.172; 2.B.239.175; 2.B.239.240; 2.B.239.244; 2.B.154.228; 2.B.154.229; 2.B.154.230; 2.B.154.231; 2.B.154.236; 2.B.154.237; 2.B.154.238; 2.B.154.239; 2.B.154.154; 2.B.154.157; 2.B.154.166; 2.B.154.169; 2.B.154.172; 2.B.154.175; 2.B.154.240; 2.B.154.244; 2.B.157.228; 2.B.157.229; 2.B.157.230; 2.B.157.231; 2.B.157.236; 2.B.157.237; 2.B.157.238; 2.B.157.239; 2.B.157.154; 2.B.157.157; 2.B.157.166; 2.B.157.169; 2.B.157.172; 2.B.157.175; 2.B.157.240; 2.B.157.244; 2.B.166.228; 2.B.166.229; 2.B.166.230; 2.B.166.231; 2.B.166.236; 2.B.166.237; 2.B.166.238; 2.B.166.239; 2.B.166.154; 2.B.166.157; 2.B.166.166; 2.B.166.169; 2.B.166.172; 2.B.166.175; 2.B.166.240; 2.B.166.244; 2.B.169.228; 2.B.169.229; 2.B.169.230; 2.B.169.231; 2.B.169.236; 2.B.169.237; 2.B.169.238; 2.B.169.239; 2.B.169.154; 2.B.169.157; 2.B.169.166; 2.B.169.169; 2.B.169.172; 2.B.169.175; 2.B.169.240; 2.B.169.244; 2.B.172.228; 2.B.172.229; 2.B.172.230; 2.B.172.231; 2.B.172.236; 2.B.172.237; 2.B.172.238; 2.B.172.239; 2.B.172.154; 2.B.172.157; 2.B.172.166; 2.B.172.169; 2.B.172.172; 2.B.172.175; 2.B.172.240; 2.B.172.244; 2.B.175.228; 2.B.175.229; 2.B.175.230; 2.B.175.231; 2.B.175.236; 2.B.175.237; 2.B.175.238; 2.B.175.239; 2.B.175.154; 2.B.175.157; 2.B.175.166; 2.B.175.169; 2.B.175.172; 2.B.175.175; 2.B.175.240; 2.B.175.244; 2.B.240.228; 2.B.240.229; 2.B.240.230; 2.B.240.231; 2.B.240.236; 2.B.240.237; 2.B.240.238; 2.B.240.239; 2.B.240.154; 2.B.240.157; 2.B.240.166; 2.B.240.169; 2.B.240.172; 2.B.240.175; 2.B.240.240; 2.B.240.244; 2.B.244.228; 2.B.244.229; 2.B.244.230; 2.B.244.231; 2.B.244.236; 2.B.244.237; 2.B.244.238; 2.B.244.239; 2.B.244.154; 2.B.244.157; 2.B.244.166; 2.B.244.169; 2.B.244.172; 2.B.244.175; 2.B.244.240; 2.B.244.244;

Prodrugs of 2.D

2.D.228.228; 2.D.228.229; 2.D.228.230; 2.D.228.231; 2.D.228.236; 2.D.228.237; 2.D.228.238; 2.D.228.239; 2.D.228.154; 2.D.228.157; 2.D.228.166; 2.D.228.169; 2.D.228.172; 2.D.228.175; 2.D.228.240; 2.D.228.244; 2.D.229.228; 2.D.229.229;

2.D.229.230; 2.D.229.231; 2.D.229.236; 2.D.229.237; 2.D.229.238; 2.D.229.239; 2.D.229.154; 2.D.229.157; 2.D.229.166; 2.D.229.169; 2.D.229.172; 2.D.229.175; 2.D.229.240; 2.D.229.244; 2.D.230.228; 2.D.230.229; 2.D.230.230; 2.D.230.231; 2.D.230.236; 2.D.230.237; 2.D.230.238; 2.D.230.239; 2.D.230.154; 2.D.230.157; 2.D.230.166; 2.D.230.169; 2.D.230.172; 2.D.230.175; 2.D.230.240; 2.D.230.244; 2.D.231.228; 2.D.231.229; 2.D.231.230; 2.D.231.231; 2.D.231.236; 2.D.231.237; 2.D.231.238; 2.D.231.239; 2.D.231.154; 2.D.231.157; 2.D.231.166; 2.D.231.169; 2.D.231.172; 2.D.231.175; 2.D.231.240; 2.D.231.244; 2.D.236.228; 2.D.236.229; 2.D.236.230; 2.D.236.231; 2.D.236.236; 2.D.236.237; 2.D.236.238; 2.D.236.239; 2.D.236.154; 2.D.236.157; 2.D.236.166; 2.D.236.169; 2.D.236.172; 2.D.236.175; 2.D.236.240; 2.D.236.244; 2.D.237.228; 2.D.237.229; 2.D.237.230; 2.D.237.231; 2.D.237.236; 2.D.237.237; 2.D.237.238; 2.D.237.239; 2.D.237.154; 2.D.237.157; 2.D.237.166; 2.D.237.169; 2.D.237.172; 2.D.237.175; 2.D.237.240; 2.D.237.244; 2.D.238.228; 2.D.238.229; 2.D.238.230; 2.D.238.231; 2.D.238.236; 2.D.238.237; 2.D.238.238; 2.D.238.239; 2.D.238.154; 2.D.238.157; 2.D.238.166; 2.D.238.169; 2.D.238.172; 2.D.238.175; 2.D.238.240; 2.D.238.244; 2.D.239.228; 2.D.239.229; 2.D.239.230; 2.D.239.231; 2.D.239.236; 2.D.239.237; 2.D.239.238; 2.D.239.239; 2.D.239.154; 2.D.239.157; 2.D.239.166; 2.D.239.169; 2.D.239.172; 2.D.239.175; 2.D.239.240; 2.D.239.244; 2.D.154.228; 2.D.154.229; 2.D.154.230; 2.D.154.231; 2.D.154.236; 2.D.154.237; 2.D.154.238; 2.D.154.239; 2.D.154.154; 2.D.154.157; 2.D.154.166; 2.D.154.169; 2.D.154.172; 2.D.154.175; 2.D.154.240; 2.D.154.244; 2.D.157.228; 2.D.157.229; 2.D.157.230; 2.D.157.231; 2.D.157.236; 2.D.157.237; 2.D.157.238; 2.D.157.239; 2.D.157.154; 2.D.157.157; 2.D.157.166; 2.D.157.169; 2.D.157.172; 2.D.157.175; 2.D.157.240; 2.D.157.244; 2.D.166.228; 2.D.166.229; 2.D.166.230; 2.D.166.231; 2.D.166.236; 2.D.166.237; 2.D.166.238; 2.D.166.239; 2.D.166.154; 2.D.166.157; 2.D.166.166; 2.D.166.169; 2.D.166.172; 2.D.166.175; 2.D.166.240; 2.D.166.244; 2.D.169.228; 2.D.169.229; 2.D.169.230; 2.D.169.231; 2.D.169.236; 2.D.169.237; 2.D.169.238; 2.D.169.239; 2.D.169.154; 2.D.169.157; 2.D.169.166; 2.D.169.169; 2.D.169.172; 2.D.169.175; 2.D.169.240; 2.D.169.244; 2.D.172.228; 2.D.172.229; 2.D.172.230; 2.D.172.231; 2.D.172.236; 2.D.172.237; 2.D.172.238; 2.D.172.239; 2.D.172.154; 2.D.172.157; 2.D.172.166; 2.D.172.169; 2.D.172.172; 2.D.172.175; 2.D.172.240; 2.D.172.244; 2.D.175.228; 2.D.175.229; 2.D.175.230; 2.D.175.231; 2.D.175.236; 2.D.175.237; 2.D.175.238; 2.D.175.239; 2.D.175.154; 2.D.175.157; 2.D.175.166; 2.D.175.169; 2.D.175.172; 2.D.175.175; 2.D.175.240; 2.D.175.244; 2.D.240.228; 2.D.240.229; 2.D.240.230; 2.D.240.231; 2.D.240.236; 2.D.240.237; 2.D.240.238; 2.D.240.239; 2.D.240.154; 2.D.240.157; 2.D.240.166; 2.D.240.169; 2.D.240.172; 2.D.240.175; 2.D.240.240; 2.D.240.244; 2.D.244.228; 2.D.244.229; 2.D.244.230; 2.D.244.231; 2.D.244.236; 2.D.244.237; 2.D.244.238; 2.D.244.239; 2.D.244.154; 2.D.244.157; 2.D.244.166; 2.D.244.169; 2.D.244.172; 2.D.244.175; 2.D.244.240; 2.D.244.244;

Prodrugs of 2.E

2.E.228.228; 2.E.228.229; 2.E.228.230; 2.E.228.231; 2.E.228.236; 2.E.228.237; 2.E.228.238; 2.E.228.239; 2.E.228.154; 2.E.228.157; 2.E.228.166; 2.E.228.169; 2.E.228.172; 2.E.228.175; 2.E.228.240; 2.E.228.244; 2.E.229.228; 2.E.229.229; 2.E.229.230; 2.E.229.231; 2.E.229.236; 2.E.229.237; 2.E.229.238; 2.E.229.239; 2.E.229.154; 2.E.229.157; 2.E.229.166;

2.E.229.169; 2.E.229.172; 2.E.229.175; 2.E.229.240; 2.E.229.244; 2.E.230.228; 2.E.230.229; 2.E.230.230; 2.E.230.231; 2.E.230.236; 2.E.230.237; 2.E.230.238; 2.E.230.239; 2.E.230.154; 2.E.230.157; 2.E.230.166; 2.E.230.169; 2.E.230.172; 2.E.230.175; 2.E.230.240; 2.E.230.244; 2.E.231.228; 2.E.231.229; 2.E.231.230; 2.E.231.231; 2.E.231.236; 2.E.231.237; 2.E.231.238; 2.E.231.239; 2.E.231.154; 2.E.231.157; 2.E.231.166; 2.E.231.169; 2.E.231.172; 2.E.231.175; 2.E.231.240; 2.E.231.244; 2.E.236.228; 2.E.236.229; 2.E.236.230; 2.E.236.231; 2.E.236.236; 2.E.236.237; 2.E.236.238; 2.E.236.239; 2.E.236.154; 2.E.236.157; 2.E.236.166; 2.E.236.169; 2.E.236.172; 2.E.236.175; 2.E.236.240; 2.E.236.244; 2.E.237.228; 2.E.237.229; 2.E.237.230; 2.E.237.231; 2.E.237.236; 2.E.237.237; 2.E.237.238; 2.E.237.239; 2.E.237.154; 2.E.237.157; 2.E.237.166; 2.E.237.169; 2.E.237.172; 2.E.237.175; 2.E.237.240; 2.E.237.244; 2.E.238.228; 2.E.238.229; 2.E.238.230; 2.E.238.231; 2.E.238.236; 2.E.238.237; 2.E.238.238; 2.E.238.239; 2.E.238.154; 2.E.238.157; 2.E.238.166; 2.E.238.169; 2.E.238.172; 2.E.238.175; 2.E.238.240; 2.E.238.244; 2.E.239.228; 2.E.239.229; 2.E.239.230; 2.E.239.231; 2.E.239.236; 2.E.239.237; 2.E.239.238; 2.E.239.239; 2.E.239.154; 2.E.239.157; 2.E.239.166; 2.E.239.169; 2.E.239.172; 2.E.239.175; 2.E.239.240; 2.E.239.244; 2.E.154.228; 2.E.154.229; 2.E.154.230; 2.E.154.231; 2.E.154.236; 2.E.154.237; 2.E.154.238; 2.E.154.239; 2.E.154.154; 2.E.154.157; 2.E.154.166; 2.E.154.169; 2.E.154.172; 2.E.154.175; 2.E.154.240; 2.E.154.244; 2.E.157.228; 2.E.157.229; 2.E.157.230; 2.E.157.231; 2.E.157.236; 2.E.157.237; 2.E.157.238; 2.E.157.239; 2.E.157.154; 2.E.157.157; 2.E.157.166; 2.E.157.169; 2.E.157.172; 2.E.157.175; 2.E.157.240; 2.E.157.244; 2.E.166.228; 2.E.166.229; 2.E.166.230; 2.E.166.231; 2.E.166.236; 2.E.166.237; 2.E.166.238; 2.E.166.239; 2.E.166.154; 2.E.166.157; 2.E.166.166; 2.E.166.169; 2.E.166.172; 2.E.166.175; 2.E.166.240; 2.E.166.244; 2.E.169.228; 2.E.169.229; 2.E.169.230; 2.E.169.231; 2.E.169.236; 2.E.169.237; 2.E.169.238; 2.E.169.239; 2.E.169.154; 2.E.169.157; 2.E.169.166; 2.E.169.169; 2.E.169.172; 2.E.169.175; 2.E.169.240; 2.E.169.244; 2.E.172.228; 2.E.172.229; 2.E.172.230; 2.E.172.231; 2.E.172.236; 2.E.172.237; 2.E.172.238; 2.E.172.239; 2.E.172.154; 2.E.172.157; 2.E.172.166; 2.E.172.169; 2.E.172.172; 2.E.172.175; 2.E.172.240; 2.E.172.244; 2.E.175.228; 2.E.175.229; 2.E.175.230; 2.E.175.231; 2.E.175.236; 2.E.175.237; 2.E.175.238; 2.E.175.239; 2.E.175.154; 2.E.175.157; 2.E.175.166; 2.E.175.169; 2.E.175.172; 2.E.175.175; 2.E.175.240; 2.E.175.244; 2.E.240.228; 2.E.240.229; 2.E.240.230; 2.E.240.231; 2.E.240.236; 2.E.240.237; 2.E.240.238; 2.E.240.239; 2.E.240.154; 2.E.240.157; 2.E.240.166; 2.E.240.169; 2.E.240.172; 2.E.240.175; 2.E.240.240; 2.E.240.244; 2.E.244.228; 2.E.244.229; 2.E.244.230; 2.E.244.231; 2.E.244.236; 2.E.244.237; 2.E.244.238; 2.E.244.239; 2.E.244.154; 2.E.244.157; 2.E.244.166; 2.E.244.169; 2.E.244.172; 2.E.244.175; 2.E.244.240; 2.E.244.244;

Prodrugs of 2.G

2.G.228.228; 2.G.228.229; 2.G.228.230; 2.G.228.231; 2.G.228.236; 2.G.228.237; 2.G.228.238; 2.G.228.239; 2.G.228.154; 2.G.228.157; 2.G.228.166; 2.G.228.169; 2.G.228.172; 2.G.228.175; 2.G.228.240; 2.G.228.244; 2.G.229.228; 2.G.229.229; 2.G.229.230; 2.G.229.231; 2.G.229.236; 2.G.229.237; 2.G.229.238; 2.G.229.239; 2.G.229.154; 2.G.229.157; 2.G.229.166; 2.G.229.169; 2.G.229.172; 2.G.229.175; 2.G.229.240; 2.G.229.244; 2.G.230.228; 2.G.230.229; 2.G.230.230; 2.G.230.231; 2.G.230.236; 2.G.230.237; 2.G.230.238; 2.G.230.239; 2.G.230.154; 2.G.230.157; 2.G.230.166; 2.G.230.169; 2.G.230.172; 2.G.230.175; 2.G.230.240; 2.G.230.244; 2.G.231.228; 2.G.231.229; 2.G.231.230; 2.G.231.231; 2.G.231.236; 2.G.231.237; 2.G.231.238; 2.G.231.239; 2.G.231.154; 2.G.231.157; 2.G.231.166; 2.G.231.169; 2.G.231.172; 2.G.231.175; 2.G.231.240; 2.G.231.244; 2.G.236.228; 2.G.236.229;

2.G.236.230; 2.G.236.231; 2.G.236.236; 2.G.236.237; 2.G.236.238; 2.G.236.239; 2.G.236.154; 2.G.236.157; 2.G.236.166; 2.G.236.169; 2.G.236.172; 2.G.236.175; 2.G.236.240; 2.G.236.244; 2.G.237.228; 2.G.237.229; 2.G.237.230; 2.G.237.231; 2.G.237.236; 2.G.237.237; 2.G.237.238; 2.G.237.239; 2.G.237.154; 2.G.237.157; 2.G.237.166; 2.G.237.169; 2.G.237.172; 2.G.237.175; 2.G.237.240; 2.G.237.244; 2.G.238.228; 2.G.238.229; 2.G.238.230; 2.G.238.231; 2.G.238.236; 2.G.238.237; 2.G.238.238; 2.G.238.239; 2.G.238.154; 2.G.238.157; 2.G.238.166; 2.G.238.169; 2.G.238.172; 2.G.238.175; 2.G.238.240; 2.G.238.244; 2.G.239.228; 2.G.239.229; 2.G.239.230; 2.G.239.231; 2.G.239.236; 2.G.239.237; 2.G.239.238; 2.G.239.239; 2.G.239.154; 2.G.239.157; 2.G.239.166; 2.G.239.169; 2.G.239.172; 2.G.239.175; 2.G.239.240; 2.G.239.244; 2.G.154.228; 2.G.154.229; 2.G.154.230; 2.G.154.231; 2.G.154.236; 2.G.154.237; 2.G.154.238; 2.G.154.239; 2.G.154.154; 2.G.154.157; 2.G.154.166; 2.G.154.169; 2.G.154.172; 2.G.154.175; 2.G.154.240; 2.G.154.244; 2.G.157.228; 2.G.157.229; 2.G.157.230; 2.G.157.231; 2.G.157.236; 2.G.157.237; 2.G.157.238; 2.G.157.239; 2.G.157.154; 2.G.157.157; 2.G.157.166; 2.G.157.169; 2.G.157.172; 2.G.157.175; 2.G.157.240; 2.G.157.244; 2.G.166.228; 2.G.166.229; 2.G.166.230; 2.G.166.231; 2.G.166.236; 2.G.166.237; 2.G.166.238; 2.G.166.239; 2.G.166.154; 2.G.166.157; 2.G.166.166; 2.G.166.169; 2.G.166.172; 2.G.166.175; 2.G.166.240; 2.G.166.244; 2.G.169.228; 2.G.169.229; 2.G.169.230; 2.G.169.231; 2.G.169.236; 2.G.169.237; 2.G.169.238; 2.G.169.239; 2.G.169.154; 2.G.169.157; 2.G.169.166; 2.G.169.169; 2.G.169.172; 2.G.169.175; 2.G.169.240; 2.G.169.244; 2.G.172.228; 2.G.172.229; 2.G.172.230; 2.G.172.231; 2.G.172.236; 2.G.172.237; 2.G.172.238; 2.G.172.239; 2.G.172.154; 2.G.172.157; 2.G.172.166; 2.G.172.169; 2.G.172.172; 2.G.172.175; 2.G.172.240; 2.G.172.244; 2.G.175.228; 2.G.175.229; 2.G.175.230; 2.G.175.231; 2.G.175.236; 2.G.175.237; 2.G.175.238; 2.G.175.239; 2.G.175.154; 2.G.175.157; 2.G.175.166; 2.G.175.169; 2.G.175.172; 2.G.175.175; 2.G.175.240; 2.G.175.244; 2.G.240.228; 2.G.240.229; 2.G.240.230; 2.G.240.231; 2.G.240.236; 2.G.240.237; 2.G.240.238; 2.G.240.239; 2.G.240.154; 2.G.240.157; 2.G.240.166; 2.G.240.169; 2.G.240.172; 2.G.240.175; 2.G.240.240; 2.G.240.244; 2.G.244.228; 2.G.244.229; 2.G.244.230; 2.G.244.231; 2.G.244.236; 2.G.244.237; 2.G.244.238; 2.G.244.239; 2.G.244.154; 2.G.244.157; 2.G.244.166; 2.G.244.169; 2.G.244.172; 2.G.244.175; 2.G.244.240; 2.G.244.244;

Prodrugs of 2.I

2.I.228.228; 2.I.228.229; 2.I.228.230; 2.I.228.231; 2.I.228.236; 2.I.228.237; 2.I.228.238; 2.I.228.239; 2.I.228.154; 2.I.228.157; 2.I.228.166; 2.I.228.169; 2.I.228.172; 2.I.228.175; 2.I.228.240; 2.I.228.244; 2.I.229.228; 2.I.229.229; 2.I.229.230; 2.I.229.231; 2.I.229.236; 2.I.229.237; 2.I.229.238; 2.I.229.239; 2.I.229.154; 2.I.229.157; 2.I.229.166; 2.I.229.169; 2.I.229.172; 2.I.229.175; 2.I.229.240; 2.I.229.244; 2.I.230.228; 2.I.230.229; 2.I.230.230; 2.I.230.231; 2.I.230.236; 2.I.230.237; 2.I.230.238; 2.I.230.239; 2.I.230.154; 2.I.230.157; 2.I.230.166; 2.I.230.169; 2.I.230.172; 2.I.230.175; 2.I.230.240; 2.I.230.244; 2.I.231.228; 2.I.231.229; 2.I.231.230; 2.I.231.231; 2.I.231.236; 2.I.231.237; 2.I.231.238; 2.I.231.239; 2.I.231.154; 2.I.231.157; 2.I.231.166; 2.I.231.169; 2.I.231.172; 2.I.231.175; 2.I.231.240; 2.I.231.244; 2.I.236.228; 2.I.236.229; 2.I.236.230; 2.I.236.231; 2.I.236.236; 2.I.236.237; 2.I.236.238; 2.I.236.239; 2.I.236.154; 2.I.236.157; 2.I.236.166; 2.I.236.169; 2.I.236.172; 2.I.236.175; 2.I.236.240; 2.I.236.244; 2.I.237.228; 2.I.237.229; 2.I.237.230; 2.I.237.231;

2.I.237.236; 2.I.237.237; 2.I.237.238; 2.I.237.239; 2.I.237.154; 2.I.237.157; 2.I.237.166; 2.I.237.169; 2.I.237.172; 2.I.237.175; 2.I.237.240; 2.I.237.244; 2.I.238.228; 2.I.238.229; 2.I.238.230; 2.I.238.231; 2.I.238.236; 2.I.238.237; 2.I.238.238; 2.I.238.239; 2.I.238.154; 2.I.238.157; 2.I.238.166; 2.I.238.169; 2.I.238.172; 2.I.238.175; 2.I.238.240; 2.I.238.244; 2.I.239.228; 2.I.239.229; 2.I.239.230; 2.I.239.231; 2.I.239.236; 2.I.239.237; 2.I.239.238; 2.I.239.239; 2.I.239.154; 2.I.239.157; 2.I.239.166; 2.I.239.169; 2.I.239.172; 2.I.239.175; 2.I.239.240; 2.I.239.244; 2.I.154.228; 2.I.154.229; 2.I.154.230; 2.I.154.231; 2.I.154.236; 2.I.154.237; 2.I.154.238; 2.I.154.239; 2.I.154.154; 2.I.154.157; 2.I.154.166; 2.I.154.169; 2.I.154.172; 2.I.154.175; 2.I.154.240; 2.I.154.244; 2.I.157.228; 2.I.157.229; 2.I.157.230; 2.I.157.231; 2.I.157.236; 2.I.157.237; 2.I.157.238; 2.I.157.239; 2.I.157.154; 2.I.157.157; 2.I.157.166; 2.I.157.169; 2.I.157.172; 2.I.157.175; 2.I.157.240; 2.I.157.244; 2.I.166.228; 2.I.166.229; 2.I.166.230; 2.I.166.231; 2.I.166.236; 2.I.166.237; 2.I.166.238; 2.I.166.239; 2.I.166.154; 2.I.166.157; 2.I.166.166; 2.I.166.169; 2.I.166.172; 2.I.166.175; 2.I.166.240; 2.I.166.244; 2.I.169.228; 2.I.169.229; 2.I.169.230; 2.I.169.231; 2.I.169.236; 2.I.169.237; 2.I.169.238; 2.I.169.239; 2.I.169.154; 2.I.169.157; 2.I.169.166; 2.I.169.169; 2.I.169.172; 2.I.169.175; 2.I.169.240; 2.I.169.244; 2.I.172.228; 2.I.172.229; 2.I.172.230; 2.I.172.231; 2.I.172.236; 2.I.172.237; 2.I.172.238; 2.I.172.239; 2.I.172.154; 2.I.172.157; 2.I.172.166; 2.I.172.169; 2.I.172.172; 2.I.172.175; 2.I.172.240; 2.I.172.244; 2.I.175.228; 2.I.175.229; 2.I.175.230; 2.I.175.231; 2.I.175.236; 2.I.175.237; 2.I.175.238; 2.I.175.239; 2.I.175.154; 2.I.175.157; 2.I.175.166; 2.I.175.169; 2.I.175.172; 2.I.175.175; 2.I.175.240; 2.I.175.244; 2.I.240.228; 2.I.240.229; 2.I.240.230; 2.I.240.231; 2.I.240.236; 2.I.240.237; 2.I.240.238; 2.I.240.239; 2.I.240.154; 2.I.240.157; 2.I.240.166; 2.I.240.169; 2.I.240.172; 2.I.240.175; 2.I.240.240; 2.I.240.244; 2.I.244.228; 2.I.244.229; 2.I.244.230; 2.I.244.231; 2.I.244.236; 2.I.244.237; 2.I.244.238; 2.I.244.239; 2.I.244.154; 2.I.244.157; 2.I.244.166; 2.I.244.169; 2.I.244.172; 2.I.244.175; 2.I.244.240; 2.I.244.244;

Prodrugs of 2.J

2.J.228.228; 2.J.228.229; 2.J.228.230; 2.J.228.231; 2.J.228.236; 2.J.228.237; 2.J.228.238; 2.J.228.239; 2.J.228.154; 2.J.228.157; 2.J.228.166; 2.J.228.169; 2.J.228.172; 2.J.228.175; 2.J.228.240; 2.J.228.244; 2.J.229.228; 2.J.229.229; 2.J.229.230; 2.J.229.231; 2.J.229.236; 2.J.229.237; 2.J.229.238; 2.J.229.239; 2.J.229.154; 2.J.229.157; 2.J.229.166; 2.J.229.169; 2.J.229.172; 2.J.229.175; 2.J.229.240; 2.J.229.244; 2.J.230.228; 2.J.230.229; 2.J.230.230; 2.J.230.231; 2.J.230.236; 2.J.230.237; 2.J.230.238; 2.J.230.239; 2.J.230.154; 2.J.230.157; 2.J.230.166; 2.J.230.169; 2.J.230.172; 2.J.230.175; 2.J.230.240; 2.J.230.244; 2.J.231.228; 2.J.231.229; 2.J.231.230; 2.J.231.231; 2.J.231.236; 2.J.231.237; 2.J.231.238; 2.J.231.239; 2.J.231.154; 2.J.231.157; 2.J.231.166; 2.J.231.169; 2.J.231.172; 2.J.231.175; 2.J.231.240; 2.J.231.244; 2.J.236.228; 2.J.236.229; 2.J.236.230; 2.J.236.231; 2.J.236.236; 2.J.236.237; 2.J.236.238; 2.J.236.239; 2.J.236.154; 2.J.236.157; 2.J.236.166; 2.J.236.169; 2.J.236.172; 2.J.236.175; 2.J.236.240; 2.J.236.244; 2.J.237.228; 2.J.237.229; 2.J.237.230; 2.J.237.231; 2.J.237.236; 2.J.237.237; 2.J.237.238; 2.J.237.239; 2.J.237.154; 2.J.237.157; 2.J.237.166; 2.J.237.169; 2.J.237.172; 2.J.237.175; 2.J.237.240; 2.J.237.244; 2.J.238.228; 2.J.238.229; 2.J.238.230; 2.J.238.231; 2.J.238.236; 2.J.238.237; 2.J.238.238; 2.J.238.239; 2.J.238.154; 2.J.238.157; 2.J.238.166; 2.J.238.169; 2.J.238.172; 2.J.238.175; 2.J.238.240; 2.J.238.244; 2.J.239.228; 2.J.239.229; 2.J.239.230; 2.J.239.231; 2.J.239.236; 2.J.239.237; 2.J.239.238; 2.J.239.239; 2.J.239.154; 2.J.239.157; 2.J.239.166; 2.J.239.169; 2.J.239.172; 2.J.239.175; 2.J.239.240; 2.J.239.244; 2.J.154.228; 2.J.154.229; 2.J.154.230; 2.J.154.231; 2.J.154.236;

2.J.154.237; 2.J.154.238; 2.J.154.239; 2.J.154.154; 2.J.154.157; 2.J.154.166; 2.J.154.169; 2.J.154.172; 2.J.154.175; 2.J.154.240; 2.J.154.244; 2.J.157.228; 2.J.157.229; 2.J.157.230; 2.J.157.231; 2.J.157.236; 2.J.157.237; 2.J.157.238; 2.J.157.239; 2.J.157.154; 2.J.157.157; 2.J.157.166; 2.J.157.169; 2.J.157.172; 2.J.157.175; 2.J.157.240; 2.J.157.244; 2.J.166.228; 2.J.166.229; 2.J.166.230; 2.J.166.231; 2.J.166.236; 2.J.166.237; 2.J.166.238; 2.J.166.239; 2.J.166.154; 2.J.166.157; 2.J.166.166; 2.J.166.169; 2.J.166.172; 2.J.166.175; 2.J.166.240; 2.J.166.244; 2.J.169.228; 2.J.169.229; 2.J.169.230; 2.J.169.231; 2.J.169.236; 2.J.169.237; 2.J.169.238; 2.J.169.239; 2.J.169.154; 2.J.169.157; 2.J.169.166; 2.J.169.169; 2.J.169.172; 2.J.169.175; 2.J.169.240; 2.J.169.244; 2.J.172.228; 2.J.172.229; 2.J.172.230; 2.J.172.231; 2.J.172.236; 2.J.172.237; 2.J.172.238; 2.J.172.239; 2.J.172.154; 2.J.172.157; 2.J.172.166; 2.J.172.169; 2.J.172.172; 2.J.172.175; 2.J.172.240; 2.J.172.244; 2.J.175.228; 2.J.175.229; 2.J.175.230; 2.J.175.231; 2.J.175.236; 2.J.175.237; 2.J.175.238; 2.J.175.239; 2.J.175.154; 2.J.175.157; 2.J.175.166; 2.J.175.169; 2.J.175.172; 2.J.175.175; 2.J.175.240; 2.J.175.244; 2.J.240.228; 2.J.240.229; 2.J.240.230; 2.J.240.231; 2.J.240.236; 2.J.240.237; 2.J.240.238; 2.J.240.239; 2.J.240.154; 2.J.240.157; 2.J.240.166; 2.J.240.169; 2.J.240.172; 2.J.240.175; 2.J.240.240; 2.J.240.244; 2.J.244.228; 2.J.244.229; 2.J.244.230; 2.J.244.231; 2.J.244.236; 2.J.244.237; 2.J.244.238; 2.J.244.239; 2.J.244.154; 2.J.244.157; 2.J.244.166; 2.J.244.169; 2.J.244.172; 2.J.244.175; 2.J.244.240; 2.J.244.244;

Prodrugs of 2.L

2.L.228.228; 2.L.228.229; 2.L.228.230; 2.L.228.231; 2.L.228.236; 2.L.228.237; 2.L.228.238; 2.L.228.239; 2.L.228.154; 2.L.228.157; 2.L.228.166; 2.L.228.169; 2.L.228.172; 2.L.228.175; 2.L.228.240; 2.L.228.244; 2.L.229.228; 2.L.229.229; 2.L.229.230; 2.L.229.231; 2.L.229.236; 2.L.229.237; 2.L.229.238; 2.L.229.239; 2.L.229.154; 2.L.229.157; 2.L.229.166; 2.L.229.169; 2.L.229.172; 2.L.229.175; 2.L.229.240; 2.L.229.244; 2.L.230.228; 2.L.230.229; 2.L.230.230; 2.L.230.231; 2.L.230.236; 2.L.230.237; 2.L.230.238; 2.L.230.239; 2.L.230.154; 2.L.230.157; 2.L.230.166; 2.L.230.169; 2.L.230.172; 2.L.230.175; 2.L.230.240; 2.L.230.244; 2.L.231.228; 2.L.231.229; 2.L.231.230; 2.L.231.231; 2.L.231.236; 2.L.231.237; 2.L.231.238; 2.L.231.239; 2.L.231.154; 2.L.231.157; 2.L.231.166; 2.L.231.169; 2.L.231.172; 2.L.231.175; 2.L.231.240; 2.L.231.244; 2.L.236.228; 2.L.236.229; 2.L.236.230; 2.L.236.231; 2.L.236.236; 2.L.236.237; 2.L.236.238; 2.L.236.239; 2.L.236.154; 2.L.236.157; 2.L.236.166; 2.L.236.169; 2.L.236.172; 2.L.236.175; 2.L.236.240; 2.L.236.244; 2.L.237.228; 2.L.237.229; 2.L.237.230; 2.L.237.231; 2.L.237.236; 2.L.237.237; 2.L.237.238; 2.L.237.239; 2.L.237.154; 2.L.237.157; 2.L.237.166; 2.L.237.169; 2.L.237.172; 2.L.237.175; 2.L.237.240; 2.L.237.244; 2.L.238.228; 2.L.238.229; 2.L.238.230; 2.L.238.231; 2.L.238.236; 2.L.238.237; 2.L.238.238; 2.L.238.239; 2.L.238.154; 2.L.238.157; 2.L.238.166; 2.L.238.169; 2.L.238.172; 2.L.238.175; 2.L.238.240; 2.L.238.244; 2.L.239.228; 2.L.239.229; 2.L.239.230; 2.L.239.231; 2.L.239.236; 2.L.239.237; 2.L.239.238; 2.L.239.239; 2.L.239.154; 2.L.239.157; 2.L.239.166; 2.L.239.169; 2.L.239.172; 2.L.239.175; 2.L.239.240; 2.L.239.244; 2.L.154.228; 2.L.154.229; 2.L.154.230; 2.L.154.231; 2.L.154.236; 2.L.154.237; 2.L.154.238; 2.L.154.239; 2.L.154.154; 2.L.154.157; 2.L.154.166; 2.L.154.169; 2.L.154.172; 2.L.154.175; 2.L.154.240; 2.L.154.244; 2.L.157.228; 2.L.157.229; 2.L.157.230; 2.L.157.231; 2.L.157.236; 2.L.157.237; 2.L.157.238; 2.L.157.239; 2.L.157.154; 2.L.157.157; 2.L.157.166; 2.L.157.169; 2.L.157.172; 2.L.157.175; 2.L.157.240; 2.L.157.244; 2.L.166.228; 2.L.166.229; 2.L.166.230; 2.L.166.231; 2.L.166.236; 2.L.166.237; 2.L.166.238; 2.L.166.239; 2.L.166.154; 2.L.166.157; 2.L.166.166; 2.L.166.169; 2.L.166.172; 2.L.166.175; 2.L.166.240; 2.L.166.244; 2.L.169.228; 2.L.169.229; 2.L.169.230; 2.L.169.231; 2.L.169.236;

2.L.169.237; 2.L.169.238; 2.L.169.239; 2.L.169.154; 2.L.169.157; 2.L.169.166; 2.L.169.169; 2.L.169.172; 2.L.169.175; 2.L.169.240; 2.L.169.244; 2.L.172.228; 2.L.172.229; 2.L.172.230; 2.L.172.231; 2.L.172.236; 2.L.172.237; 2.L.172.238; 2.L.172.239; 2.L.172.154; 2.L.172.157; 2.L.172.166; 2.L.172.169; 2.L.172.172; 2.L.172.175; 2.L.172.240; 2.L.172.244; 2.L.175.228; 2.L.175.229; 2.L.175.230; 2.L.175.231; 2.L.175.236; 2.L.175.237; 2.L.175.238; 2.L.175.239; 2.L.175.154; 2.L.175.157; 2.L.175.166; 2.L.175.169; 2.L.175.172; 2.L.175.175; 2.L.175.240; 2.L.175.244; 2.L.240.228; 2.L.240.229; 2.L.240.230; 2.L.240.231; 2.L.240.236; 2.L.240.237; 2.L.240.238; 2.L.240.239; 2.L.240.154; 2.L.240.157; 2.L.240.166; 2.L.240.169; 2.L.240.172; 2.L.240.175; 2.L.240.240; 2.L.240.244; 2.L.244.228; 2.L.244.229; 2.L.244.230; 2.L.244.231; 2.L.244.236; 2.L.244.237; 2.L.244.238; 2.L.244.239; 2.L.244.154; 2.L.244.157; 2.L.244.166; 2.L.244.169; 2.L.244.172; 2.L.244.175; 2.L.244.240; 2.L.244.244;

Prodrugs of 2.O

2.O.228.228; 2.O.228.229; 2.O.228.230; 2.O.228.231; 2.O.228.236; 2.O.228.237; 2.O.228.238; 2.O.228.239; 2.O.228.154; 2.O.228.157; 2.O.228.166; 2.O.228.169; 2.O.228.172; 2.O.228.175; 2.O.228.240; 2.O.228.244; 2.O.229.228; 2.O.229.229; 2.O.229.230; 2.O.229.231; 2.O.229.236; 2.O.229.237; 2.O.229.238; 2.O.229.239; 2.O.229.154; 2.O.229.157; 2.O.229.166; 2.O.229.169; 2.O.229.172; 2.O.229.175; 2.O.229.240; 2.O.229.244; 2.O.230.228; 2.O.230.229; 2.O.230.230; 2.O.230.231; 2.O.230.236; 2.O.230.237; 2.O.230.238; 2.O.230.239; 2.O.230.154; 2.O.230.157; 2.O.230.166; 2.O.230.169; 2.O.230.172; 2.O.230.175; 2.O.230.240; 2.O.230.244; 2.O.231.228; 2.O.231.229; 2.O.231.230; 2.O.231.231; 2.O.231.236; 2.O.231.237; 2.O.231.238; 2.O.231.239; 2.O.231.154; 2.O.231.157; 2.O.231.166; 2.O.231.169; 2.O.231.172; 2.O.231.175; 2.O.231.240; 2.O.231.244; 2.O.236.228; 2.O.236.229; 2.O.236.230; 2.O.236.231; 2.O.236.236; 2.O.236.237; 2.O.236.238; 2.O.236.239; 2.O.236.154; 2.O.236.157; 2.O.236.166; 2.O.236.169; 2.O.236.172; 2.O.236.175; 2.O.236.240; 2.O.236.244; 2.O.237.228; 2.O.237.229; 2.O.237.230; 2.O.237.231; 2.O.237.236; 2.O.237.237; 2.O.237.238; 2.O.237.239; 2.O.237.154; 2.O.237.157; 2.O.237.166; 2.O.237.169; 2.O.237.172; 2.O.237.175; 2.O.237.240; 2.O.237.244; 2.O.238.228; 2.O.238.229; 2.O.238.230; 2.O.238.231; 2.O.238.236; 2.O.238.237; 2.O.238.238; 2.O.238.239; 2.O.238.154; 2.O.238.157; 2.O.238.166; 2.O.238.169; 2.O.238.172; 2.O.238.175; 2.O.238.240; 2.O.238.244; 2.O.239.228; 2.O.239.229; 2.O.239.230; 2.O.239.231; 2.O.239.236; 2.O.239.237; 2.O.239.238; 2.O.239.239; 2.O.239.154; 2.O.239.157; 2.O.239.166; 2.O.239.169; 2.O.239.172; 2.O.239.175; 2.O.239.240; 2.O.239.244; 2.O.154.228; 2.O.154.229; 2.O.154.230; 2.O.154.231; 2.O.154.236; 2.O.154.237; 2.O.154.238; 2.O.154.239; 2.O.154.154; 2.O.154.157; 2.O.154.166; 2.O.154.169; 2.O.154.172; 2.O.154.175; 2.O.154.240; 2.O.154.244; 2.O.157.228; 2.O.157.229; 2.O.157.230; 2.O.157.231; 2.O.157.236; 2.O.157.237; 2.O.157.238; 2.O.157.239; 2.O.157.154; 2.O.157.157; 2.O.157.166; 2.O.157.169; 2.O.157.172; 2.O.157.175; 2.O.157.240; 2.O.157.244; 2.O.166.228; 2.O.166.229; 2.O.166.230; 2.O.166.231; 2.O.166.236; 2.O.166.237; 2.O.166.238; 2.O.166.239; 2.O.166.154; 2.O.166.157; 2.O.166.166; 2.O.166.169; 2.O.166.172; 2.O.166.175; 2.O.166.240; 2.O.166.244; 2.O.169.228; 2.O.169.229; 2.O.169.230; 2.O.169.231; 2.O.169.236; 2.O.169.237; 2.O.169.238; 2.O.169.239; 2.O.169.154; 2.O.169.157; 2.O.169.166; 2.O.169.169; 2.O.169.172; 2.O.169.175; 2.O.169.240; 2.O.169.244; 2.O.172.228; 2.O.172.229; 2.O.172.230; 2.O.172.231; 2.O.172.236; 2.O.172.237;

2.O.172.238; 2.O.172.239; 2.O.172.154; 2.O.172.157; 2.O.172.166; 2.O.172.169; 2.O.172.172; 2.O.172.175; 2.O.172.240; 2.O.172.244; 2.O.175.228; 2.O.175.229; 2.O.175.230; 2.O.175.231; 2.O.175.236; 2.O.175.237; 2.O.175.238; 2.O.175.239; 2.O.175.154; 2.O.175.157; 2.O.175.166; 2.O.175.169; 2.O.175.172; 2.O.175.175; 2.O.175.240; 2.O.175.244; 2.O.240.228; 2.O.240.229; 2.O.240.230; 2.O.240.231; 2.O.240.236; 2.O.240.237; 2.O.240.238; 2.O.240.239; 2.O.240.154; 2.O.240.157; 2.O.240.166; 2.O.240.169; 2.O.240.172; 2.O.240.175; 2.O.240.240; 2.O.240.244; 2.O.244.228; 2.O.244.229; 2.O.244.230; 2.O.244.231; 2.O.244.236; 2.O.244.237; 2.O.244.238; 2.O.244.239; 2.O.244.154; 2.O.244.157; 2.O.244.166; 2.O.244.169; 2.O.244.172; 2.O.244.175; 2.O.244.240; 2.O.244.244;

Prodrugs of 2.P

2.P.228.228; 2.P.228.229; 2.P.228.230; 2.P.228.231; 2.P.228.236; 2.P.228.237; 2.P.228.238; 2.P.228.239; 2.P.228.154; 2.P.228.157; 2.P.228.166; 2.P.228.169; 2.P.228.172; 2.P.228.175; 2.P.228.240; 2.P.228.244; 2.P.229.228; 2.P.229.229; 2.P.229.230; 2.P.229.231; 2.P.229.236; 2.P.229.237; 2.P.229.238; 2.P.229.239; 2.P.229.154; 2.P.229.157; 2.P.229.166; 2.P.229.169; 2.P.229.172; 2.P.229.175; 2.P.229.240; 2.P.229.244; 2.P.230.228; 2.P.230.229; 2.P.230.230; 2.P.230.231; 2.P.230.236; 2.P.230.237; 2.P.230.238; 2.P.230.239; 2.P.230.154; 2.P.230.157; 2.P.230.166; 2.P.230.169; 2.P.230.172; 2.P.230.175; 2.P.230.240; 2.P.230.244; 2.P.231.228; 2.P.231.229; 2.P.231.230; 2.P.231.231; 2.P.231.236; 2.P.231.237; 2.P.231.238; 2.P.231.239; 2.P.231.154; 2.P.231.157; 2.P.231.166; 2.P.231.169; 2.P.231.172; 2.P.231.175; 2.P.231.240; 2.P.231.244; 2.P.236.228; 2.P.236.229; 2.P.236.230; 2.P.236.231; 2.P.236.236; 2.P.236.237; 2.P.236.238; 2.P.236.239; 2.P.236.154; 2.P.236.157; 2.P.236.166; 2.P.236.169; 2.P.236.172; 2.P.236.175; 2.P.236.240; 2.P.236.244; 2.P.237.228; 2.P.237.229; 2.P.237.230; 2.P.237.231; 2.P.237.236; 2.P.237.237; 2.P.237.238; 2.P.237.239; 2.P.237.154; 2.P.237.157; 2.P.237.166; 2.P.237.169; 2.P.237.172; 2.P.237.175; 2.P.237.240; 2.P.237.244; 2.P.238.228; 2.P.238.229; 2.P.238.230; 2.P.238.231; 2.P.238.236; 2.P.238.237; 2.P.238.238; 2.P.238.239; 2.P.238.154; 2.P.238.157; 2.P.238.166; 2.P.238.169; 2.P.238.172; 2.P.238.175; 2.P.238.240; 2.P.238.244; 2.P.239.228; 2.P.239.229; 2.P.239.230; 2.P.239.231; 2.P.239.236; 2.P.239.237; 2.P.239.238; 2.P.239.239; 2.P.239.154; 2.P.239.157; 2.P.239.166; 2.P.239.169; 2.P.239.172; 2.P.239.175; 2.P.239.240; 2.P.239.244; 2.P.154.228; 2.P.154.229; 2.P.154.230; 2.P.154.231; 2.P.154.236; 2.P.154.237; 2.P.154.238; 2.P.154.239; 2.P.154.154; 2.P.154.157; 2.P.154.166; 2.P.154.169; 2.P.154.172; 2.P.154.175; 2.P.154.240; 2.P.154.244; 2.P.157.228; 2.P.157.229; 2.P.157.230; 2.P.157.231; 2.P.157.236; 2.P.157.237; 2.P.157.238; 2.P.157.239; 2.P.157.154; 2.P.157.157; 2.P.157.166; 2.P.157.169; 2.P.157.172; 2.P.157.175; 2.P.157.240; 2.P.157.244; 2.P.166.228; 2.P.166.229; 2.P.166.230; 2.P.166.231; 2.P.166.236; 2.P.166.237; 2.P.166.238; 2.P.166.239; 2.P.166.154; 2.P.166.157; 2.P.166.166; 2.P.166.169; 2.P.166.172; 2.P.166.175; 2.P.166.240; 2.P.166.244; 2.P.169.228; 2.P.169.229; 2.P.169.230; 2.P.169.231; 2.P.169.236; 2.P.169.237; 2.P.169.238; 2.P.169.239; 2.P.169.154; 2.P.169.157; 2.P.169.166; 2.P.169.169; 2.P.169.172; 2.P.169.175; 2.P.169.240; 2.P.169.244; 2.P.172.228; 2.P.172.229; 2.P.172.230; 2.P.172.231; 2.P.172.236; 2.P.172.237; 2.P.172.238; 2.P.172.239; 2.P.172.154; 2.P.172.157; 2.P.172.166; 2.P.172.169; 2.P.172.172; 2.P.172.175; 2.P.172.240; 2.P.172.244; 2.P.175.228; 2.P.175.229; 2.P.175.230; 2.P.175.231; 2.P.175.236; 2.P.175.237; 2.P.175.238; 2.P.175.239; 2.P.175.154; 2.P.175.157; 2.P.175.166; 2.P.175.169; 2.P.175.172; 2.P.175.175; 2.P.175.240; 2.P.175.244; 2.P.240.228; 2.P.240.229; 2.P.240.230; 2.P.240.231; 2.P.240.236; 2.P.240.237; 2.P.240.238; 2.P.240.239; 2.P.240.154; 2.P.240.157; 2.P.240.166; 2.P.240.169; 2.P.240.172;

2.P.240.175; 2.P.240.240; 2.P.240.244; 2.P.244.228; 2.P.244.229; 2.P.244.230; 2.P.244.231; 2.P.244.236; 2.P.244.237; 2.P.244.238; 2.P.244.239; 2.P.244.154; 2.P.244.157; 2.P.244.166; 2.P.244.169; 2.P.244.172; 2.P.244.175; 2.P.244.240; 2.P.244.244;

Prodrugs of 2.U

2.U.228.228; 2.U.228.229; 2.U.228.230; 2.U.228.231; 2.U.228.236; 2.U.228.237; 2.U.228.238; 2.U.228.239; 2.U.228.154; 2.U.228.157; 2.U.228.166; 2.U.228.169; 2.U.228.172; 2.U.228.175; 2.U.228.240; 2.U.228.244; 2.U.229.228; 2.U.229.229; 2.U.229.230; 2.U.229.231; 2.U.229.236; 2.U.229.237; 2.U.229.238; 2.U.229.239; 2.U.229.154; 2.U.229.157; 2.U.229.166; 2.U.229.169; 2.U.229.172; 2.U.229.175; 2.U.229.240; 2.U.229.244; 2.U.230.228; 2.U.230.229; 2.U.230.230; 2.U.230.231; 2.U.230.236; 2.U.230.237; 2.U.230.238; 2.U.230.239; 2.U.230.154; 2.U.230.157; 2.U.230.166; 2.U.230.169; 2.U.230.172; 2.U.230.175; 2.U.230.240; 2.U.230.244; 2.U.231.228; 2.U.231.229; 2.U.231.230; 2.U.231.231; 2.U.231.236; 2.U.231.237; 2.U.231.238; 2.U.231.239; 2.U.231.154; 2.U.231.157; 2.U.231.166; 2.U.231.169; 2.U.231.172; 2.U.231.175; 2.U.231.240; 2.U.231.244; 2.U.236.228; 2.U.236.229; 2.U.236.230; 2.U.236.231; 2.U.236.236; 2.U.236.237; 2.U.236.238; 2.U.236.239; 2.U.236.154; 2.U.236.157; 2.U.236.166; 2.U.236.169; 2.U.236.172; 2.U.236.175; 2.U.236.240; 2.U.236.244; 2.U.237.228; 2.U.237.229; 2.U.237.230; 2.U.237.231; 2.U.237.236; 2.U.237.237; 2.U.237.238; 2.U.237.239; 2.U.237.154; 2.U.237.157; 2.U.237.166; 2.U.237.169; 2.U.237.172; 2.U.237.175; 2.U.237.240; 2.U.237.244; 2.U.238.228; 2.U.238.229; 2.U.238.230; 2.U.238.231; 2.U.238.236; 2.U.238.237; 2.U.238.238; 2.U.238.239; 2.U.238.154; 2.U.238.157; 2.U.238.166; 2.U.238.169; 2.U.238.172; 2.U.238.175; 2.U.238.240; 2.U.238.244; 2.U.239.228; 2.U.239.229; 2.U.239.230; 2.U.239.231; 2.U.239.236; 2.U.239.237; 2.U.239.238; 2.U.239.239; 2.U.239.154; 2.U.239.157; 2.U.239.166; 2.U.239.169; 2.U.239.172; 2.U.239.175; 2.U.239.240; 2.U.239.244; 2.U.154.228; 2.U.154.229; 2.U.154.230; 2.U.154.231; 2.U.154.236; 2.U.154.237; 2.U.154.238; 2.U.154.239; 2.U.154.154; 2.U.154.157; 2.U.154.166; 2.U.154.169; 2.U.154.172; 2.U.154.175; 2.U.154.240; 2.U.154.244; 2.U.157.228; 2.U.157.229; 2.U.157.230; 2.U.157.231; 2.U.157.236; 2.U.157.237; 2.U.157.238; 2.U.157.239; 2.U.157.154; 2.U.157.157; 2.U.157.166; 2.U.157.169; 2.U.157.172; 2.U.157.175; 2.U.157.240; 2.U.157.244; 2.U.166.228; 2.U.166.229; 2.U.166.230; 2.U.166.231; 2.U.166.236; 2.U.166.237; 2.U.166.238; 2.U.166.239; 2.U.166.154; 2.U.166.157; 2.U.166.166; 2.U.166.169; 2.U.166.172; 2.U.166.175; 2.U.166.240; 2.U.166.244; 2.U.169.228; 2.U.169.229; 2.U.169.230; 2.U.169.231; 2.U.169.236; 2.U.169.237; 2.U.169.238; 2.U.169.239; 2.U.169.154; 2.U.169.157; 2.U.169.166; 2.U.169.169; 2.U.169.172; 2.U.169.175; 2.U.169.240; 2.U.169.244; 2.U.172.228; 2.U.172.229; 2.U.172.230; 2.U.172.231; 2.U.172.236; 2.U.172.237; 2.U.172.238; 2.U.172.239; 2.U.172.154; 2.U.172.157; 2.U.172.166; 2.U.172.169; 2.U.172.172; 2.U.172.175; 2.U.172.240; 2.U.172.244; 2.U.175.228; 2.U.175.229; 2.U.175.230; 2.U.175.231; 2.U.175.236; 2.U.175.237; 2.U.175.238; 2.U.175.239; 2.U.175.154; 2.U.175.157; 2.U.175.166; 2.U.175.169; 2.U.175.172; 2.U.175.175; 2.U.175.240; 2.U.175.244; 2.U.240.228; 2.U.240.229; 2.U.240.230; 2.U.240.231; 2.U.240.236; 2.U.240.237; 2.U.240.238; 2.U.240.239; 2.U.240.154; 2.U.240.157; 2.U.240.166; 2.U.240.169; 2.U.240.172; 2.U.240.175; 2.U.240.240; 2.U.240.244; 2.U.244.228; 2.U.244.229; 2.U.244.230; 2.U.244.231; 2.U.244.236; 2.U.244.237;

2.U.244.238; 2.U.244.239; 2.U.244.154; 2.U.244.157; 2.U.244.166; 2.U.244.169; 2.U.244.172; 2.U.244.175; 2.U.244.240; 2.U.244.244;

Prodrugs of 2.W

2.W.228.228; 2.W.228.229; 2.W.228.230; 2.W.228.231; 2.W.228.236; 2.W.228.237; 2.W.228.238; 2.W.228.239; 2.W.228.154; 2.W.228.157; 2.W.228.166; 2.W.228.169; 2.W.228.172; 2.W.228.175; 2.W.228.240; 2.W.228.244; 2.W.229.228; 2.W.229.229; 2.W.229.230; 2.W.229.231; 2.W.229.236; 2.W.229.237; 2.W.229.238; 2.W.229.239; 2.W.229.154; 2.W.229.157; 2.W.229.166; 2.W.229.169; 2.W.229.172; 2.W.229.175; 2.W.229.240; 2.W.229.244; 2.W.230.228; 2.W.230.229; 2.W.230.230; 2.W.230.231; 2.W.230.236; 2.W.230.237; 2.W.230.238; 2.W.230.239; 2.W.230.154; 2.W.230.157; 2.W.230.166; 2.W.230.169; 2.W.230.172; 2.W.230.175; 2.W.230.240; 2.W.230.244; 2.W.231.228; 2.W.231.229; 2.W.231.230; 2.W.231.231; 2.W.231.236; 2.W.231.237; 2.W.231.238; 2.W.231.239; 2.W.231.154; 2.W.231.157; 2.W.231.166; 2.W.231.169; 2.W.231.172; 2.W.231.175; 2.W.231.240; 2.W.231.244; 2.W.236.228; 2.W.236.229; 2.W.236.230; 2.W.236.231; 2.W.236.236; 2.W.236.237; 2.W.236.238; 2.W.236.239; 2.W.236.154; 2.W.236.157; 2.W.236.166; 2.W.236.169; 2.W.236.172; 2.W.236.175; 2.W.236.240; 2.W.236.244; 2.W.237.228; 2.W.237.229; 2.W.237.230; 2.W.237.231; 2.W.237.236; 2.W.237.237; 2.W.237.238; 2.W.237.239; 2.W.237.154; 2.W.237.157; 2.W.237.166; 2.W.237.169; 2.W.237.172; 2.W.237.175; 2.W.237.240; 2.W.237.244; 2.W.238.228; 2.W.238.229; 2.W.238.230; 2.W.238.231; 2.W.238.236; 2.W.238.237; 2.W.238.238; 2.W.238.239; 2.W.238.154; 2.W.238.157; 2.W.238.166; 2.W.238.169; 2.W.238.172; 2.W.238.175; 2.W.238.240; 2.W.238.244; 2.W.239.228; 2.W.239.229; 2.W.239.230; 2.W.239.231; 2.W.239.236; 2.W.239.237; 2.W.239.238; 2.W.239.239; 2.W.239.154; 2.W.239.157; 2.W.239.166; 2.W.239.169; 2.W.239.172; 2.W.239.175; 2.W.239.240; 2.W.239.244; 2.W.154.228; 2.W.154.229; 2.W.154.230; 2.W.154.231; 2.W.154.236; 2.W.154.237; 2.W.154.238; 2.W.154.239; 2.W.154.154; 2.W.154.157; 2.W.154.166; 2.W.154.169; 2.W.154.172; 2.W.154.175; 2.W.154.240; 2.W.154.244; 2.W.157.228; 2.W.157.229; 2.W.157.230; 2.W.157.231; 2.W.157.236; 2.W.157.237; 2.W.157.238; 2.W.157.239; 2.W.157.154; 2.W.157.157; 2.W.157.166; 2.W.157.169; 2.W.157.172; 2.W.157.175; 2.W.157.240; 2.W.157.244; 2.W.166.228; 2.W.166.229; 2.W.166.230; 2.W.166.231; 2.W.166.236; 2.W.166.237; 2.W.166.238; 2.W.166.239; 2.W.166.154; 2.W.166.157; 2.W.166.166; 2.W.166.169; 2.W.166.172; 2.W.166.175; 2.W.166.240; 2.W.166.244; 2.W.169.228; 2.W.169.229; 2.W.169.230; 2.W.169.231; 2.W.169.236; 2.W.169.237; 2.W.169.238; 2.W.169.239; 2.W.169.154; 2.W.169.157; 2.W.169.166; 2.W.169.169; 2.W.169.172; 2.W.169.175; 2.W.169.240; 2.W.169.244; 2.W.172.228; 2.W.172.229; 2.W.172.230; 2.W.172.231; 2.W.172.236; 2.W.172.237; 2.W.172.238; 2.W.172.239; 2.W.172.154; 2.W.172.157; 2.W.172.166; 2.W.172.169; 2.W.172.172; 2.W.172.175; 2.W.172.240; 2.W.172.244; 2.W.175.228; 2.W.175.229; 2.W.175.230; 2.W.175.231; 2.W.175.236; 2.W.175.237; 2.W.175.238; 2.W.175.239; 2.W.175.154; 2.W.175.157; 2.W.175.166; 2.W.175.169; 2.W.175.172; 2.W.175.175; 2.W.175.240; 2.W.175.244; 2.W.240.228; 2.W.240.229; 2.W.240.230; 2.W.240.231; 2.W.240.236; 2.W.240.237; 2.W.240.238; 2.W.240.239; 2.W.240.154; 2.W.240.157; 2.W.240.166; 2.W.240.169; 2.W.240.172; 2.W.240.175; 2.W.240.240; 2.W.240.244; 2.W.244.228; 2.W.244.229; 2.W.244.230; 2.W.244.231; 2.W.244.236; 2.W.244.237;

2.W.244.238; 2.W.244.239; 2.W.244.154; 2.W.244.157; 2.W.244.166; 2.W.244.169; 2.W.244.172; 2.W.244.175; 2.W.244.240; 2.W.244.244;

Prodrugs of 2.Y

2.Y.228.228; 2.Y.228.229; 2.Y.228.230; 2.Y.228.231; 2.Y.228.236; 2.Y.228.237; 2.Y.228.238; 2.Y.228.239; 2.Y.228.154; 2.Y.228.157; 2.Y.228.166; 2.Y.228.169; 2.Y.228.172; 2.Y.228.175; 2.Y.228.240; 2.Y.228.244; 2.Y.229.228; 2.Y.229.229; 2.Y.229.230; 2.Y.229.231; 2.Y.229.236; 2.Y.229.237; 2.Y.229.238; 2.Y.229.239; 2.Y.229.154; 2.Y.229.157; 2.Y.229.166; 2.Y.229.169; 2.Y.229.172; 2.Y.229.175; 2.Y.229.240; 2.Y.229.244; 2.Y.230.228; 2.Y.230.229; 2.Y.230.230; 2.Y.230.231; 2.Y.230.236; 2.Y.230.237; 2.Y.230.238; 2.Y.230.239; 2.Y.230.154; 2.Y.230.157; 2.Y.230.166; 2.Y.230.169; 2.Y.230.172; 2.Y.230.175; 2.Y.230.240; 2.Y.230.244; 2.Y.231.228; 2.Y.231.229; 2.Y.231.230; 2.Y.231.231; 2.Y.231.236; 2.Y.231.237; 2.Y.231.238; 2.Y.231.239; 2.Y.231.154; 2.Y.231.157; 2.Y.231.166; 2.Y.231.169; 2.Y.231.172; 2.Y.231.175; 2.Y.231.240; 2.Y.231.244; 2.Y.236.228; 2.Y.236.229; 2.Y.236.230; 2.Y.236.231; 2.Y.236.236; 2.Y.236.237; 2.Y.236.238; 2.Y.236.239; 2.Y.236.154; 2.Y.236.157; 2.Y.236.166; 2.Y.236.169; 2.Y.236.172; 2.Y.236.175; 2.Y.236.240; 2.Y.236.244; 2.Y.237.228; 2.Y.237.229; 2.Y.237.230; 2.Y.237.231; 2.Y.237.236; 2.Y.237.237; 2.Y.237.238; 2.Y.237.239; 2.Y.237.154; 2.Y.237.157; 2.Y.237.166; 2.Y.237.169; 2.Y.237.172; 2.Y.237.175; 2.Y.237.240; 2.Y.237.244; 2.Y.238.228; 2.Y.238.229; 2.Y.238.230; 2.Y.238.231; 2.Y.238.236; 2.Y.238.237; 2.Y.238.238; 2.Y.238.239; 2.Y.238.154; 2.Y.238.157; 2.Y.238.166; 2.Y.238.169; 2.Y.238.172; 2.Y.238.175; 2.Y.238.240; 2.Y.238.244; 2.Y.239.228; 2.Y.239.229; 2.Y.239.230; 2.Y.239.231; 2.Y.239.236; 2.Y.239.237; 2.Y.239.238; 2.Y.239.239; 2.Y.239.154; 2.Y.239.157; 2.Y.239.166; 2.Y.239.169; 2.Y.239.172; 2.Y.239.175; 2.Y.239.240; 2.Y.239.244; 2.Y.154.228; 2.Y.154.229; 2.Y.154.230; 2.Y.154.231; 2.Y.154.236; 2.Y.154.237; 2.Y.154.238; 2.Y.154.239; 2.Y.154.154; 2.Y.154.157; 2.Y.154.166; 2.Y.154.169; 2.Y.154.172; 2.Y.154.175; 2.Y.154.240; 2.Y.154.244; 2.Y.157.228; 2.Y.157.229; 2.Y.157.230; 2.Y.157.231; 2.Y.157.236; 2.Y.157.237; 2.Y.157.238; 2.Y.157.239; 2.Y.157.154; 2.Y.157.157; 2.Y.157.166; 2.Y.157.169; 2.Y.157.172; 2.Y.157.175; 2.Y.157.240; 2.Y.157.244; 2.Y.166.228; 2.Y.166.229; 2.Y.166.230; 2.Y.166.231; 2.Y.166.236; 2.Y.166.237; 2.Y.166.238; 2.Y.166.239; 2.Y.166.154; 2.Y.166.157; 2.Y.166.166; 2.Y.166.169; 2.Y.166.172; 2.Y.166.175; 2.Y.166.240; 2.Y.166.244; 2.Y.169.228; 2.Y.169.229; 2.Y.169.230; 2.Y.169.231; 2.Y.169.236; 2.Y.169.237; 2.Y.169.238; 2.Y.169.239; 2.Y.169.154; 2.Y.169.157; 2.Y.169.166; 2.Y.169.169; 2.Y.169.172; 2.Y.169.175; 2.Y.169.240; 2.Y.169.244; 2.Y.172.228; 2.Y.172.229; 2.Y.172.230; 2.Y.172.231; 2.Y.172.236; 2.Y.172.237; 2.Y.172.238; 2.Y.172.239; 2.Y.172.154; 2.Y.172.157; 2.Y.172.166; 2.Y.172.169; 2.Y.172.172; 2.Y.172.175; 2.Y.172.240; 2.Y.172.244; 2.Y.175.228; 2.Y.175.229; 2.Y.175.230; 2.Y.175.231; 2.Y.175.236; 2.Y.175.237; 2.Y.175.238; 2.Y.175.239; 2.Y.175.154; 2.Y.175.157; 2.Y.175.166; 2.Y.175.169; 2.Y.175.172; 2.Y.175.175; 2.Y.175.240; 2.Y.175.244; 2.Y.240.228; 2.Y.240.229; 2.Y.240.230; 2.Y.240.231; 2.Y.240.236; 2.Y.240.237; 2.Y.240.238; 2.Y.240.239; 2.Y.240.154; 2.Y.240.157; 2.Y.240.166; 2.Y.240.169; 2.Y.240.172; 2.Y.240.175; 2.Y.240.240; 2.Y.240.244; 2.Y.244.228; 2.Y.244.229; 2.Y.244.230; 2.Y.244.231; 2.Y.244.236; 2.Y.244.237;

2.Y.244.238; 2.Y.244.239; 2.Y.244.154; 2.Y.244.157; 2.Y.244.166; 2.Y.244.169; 2.Y.244.172; 2.Y.244.175; 2.Y.244.240; 2.Y.244.244;

Prodrugs of 3.B

3.B.228.228; 3.B.228.229; 3.B.228.230; 3.B.228.231; 3.B.228.236; 3.B.228.237; 3.B.228.238; 3.B.228.239; 3.B.228.154; 3.B.228.157; 3.B.228.166; 3.B.228.169; 3.B.228.172; 3.B.228.175; 3.B.228.240; 3.B.228.244; 3.B.229.228; 3.B.229.229; 3.B.229.230; 3.B.229.231; 3.B.229.236; 3.B.229.237; 3.B.229.238; 3.B.229.239; 3.B.229.154; 3.B.229.157; 3.B.229.166; 3.B.229.169; 3.B.229.172; 3.B.229.175; 3.B.229.240; 3.B.229.244; 3.B.230.228; 3.B.230.229; 3.B.230.230; 3.B.230.231; 3.B.230.236; 3.B.230.237; 3.B.230.238; 3.B.230.239; 3.B.230.154; 3.B.230.157; 3.B.230.166; 3.B.230.169; 3.B.230.172; 3.B.230.175; 3.B.230.240; 3.B.230.244; 3.B.231.228; 3.B.231.229; 3.B.231.230; 3.B.231.231; 3.B.231.236; 3.B.231.237; 3.B.231.238; 3.B.231.239; 3.B.231.154; 3.B.231.157; 3.B.231.166; 3.B.231.169; 3.B.231.172; 3.B.231.175; 3.B.231.240; 3.B.231.244; 3.B.236.228; 3.B.236.229; 3.B.236.230; 3.B.236.231; 3.B.236.236; 3.B.236.237; 3.B.236.238; 3.B.236.239; 3.B.236.154; 3.B.236.157; 3.B.236.166; 3.B.236.169; 3.B.236.172; 3.B.236.175; 3.B.236.240; 3.B.236.244; 3.B.237.228; 3.B.237.229; 3.B.237.230; 3.B.237.231; 3.B.237.236; 3.B.237.237; 3.B.237.238; 3.B.237.239; 3.B.237.154; 3.B.237.157; 3.B.237.166; 3.B.237.169; 3.B.237.172; 3.B.237.175; 3.B.237.240; 3.B.237.244; 3.B.238.228; 3.B.238.229; 3.B.238.230; 3.B.238.231; 3.B.238.236; 3.B.238.237; 3.B.238.238; 3.B.238.239; 3.B.238.154; 3.B.238.157; 3.B.238.166; 3.B.238.169; 3.B.238.172; 3.B.238.175; 3.B.238.240; 3.B.238.244; 3.B.239.228; 3.B.239.229; 3.B.239.230; 3.B.239.231; 3.B.239.236; 3.B.239.237; 3.B.239.238; 3.B.239.239; 3.B.239.154; 3.B.239.157; 3.B.239.166; 3.B.239.169; 3.B.239.172; 3.B.239.175; 3.B.239.240; 3.B.239.244; 3.B.154.228; 3.B.154.229; 3.B.154.230; 3.B.154.231; 3.B.154.236; 3.B.154.237; 3.B.154.238; 3.B.154.239; 3.B.154.154; 3.B.154.157; 3.B.154.166; 3.B.154.169; 3.B.154.172; 3.B.154.175; 3.B.154.240; 3.B.154.244; 3.B.157.228; 3.B.157.229; 3.B.157.230; 3.B.157.231; 3.B.157.236; 3.B.157.237; 3.B.157.238; 3.B.157.239; 3.B.157.154; 3.B.157.157; 3.B.157.166; 3.B.157.169; 3.B.157.172; 3.B.157.175; 3.B.157.240; 3.B.157.244; 3.B.166.228; 3.B.166.229; 3.B.166.230; 3.B.166.231; 3.B.166.236; 3.B.166.237; 3.B.166.238; 3.B.166.239; 3.B.166.154; 3.B.166.157; 3.B.166.166; 3.B.166.169; 3.B.166.172; 3.B.166.175; 3.B.166.240; 3.B.166.244; 3.B.169.228; 3.B.169.229; 3.B.169.230; 3.B.169.231; 3.B.169.236; 3.B.169.237; 3.B.169.238; 3.B.169.239; 3.B.169.154; 3.B.169.157; 3.B.169.166; 3.B.169.169; 3.B.169.172; 3.B.169.175; 3.B.169.240; 3.B.169.244; 3.B.172.228; 3.B.172.229; 3.B.172.230; 3.B.172.231; 3.B.172.236; 3.B.172.237; 3.B.172.238; 3.B.172.239; 3.B.172.154; 3.B.172.157; 3.B.172.166; 3.B.172.169; 3.B.172.172; 3.B.172.175; 3.B.172.240; 3.B.172.244; 3.B.175.228; 3.B.175.229; 3.B.175.230; 3.B.175.231; 3.B.175.236; 3.B.175.237; 3.B.175.238; 3.B.175.239; 3.B.175.154; 3.B.175.157; 3.B.175.166; 3.B.175.169; 3.B.175.172; 3.B.175.175; 3.B.175.240; 3.B.175.244; 3.B.240.228; 3.B.240.229; 3.B.240.230; 3.B.240.231; 3.B.240.236; 3.B.240.237; 3.B.240.238; 3.B.240.239; 3.B.240.154; 3.B.240.157; 3.B.240.166; 3.B.240.169; 3.B.240.172; 3.B.240.175; 3.B.240.240; 3.B.240.244; 3.B.244.228; 3.B.244.229; 3.B.244.230; 3.B.244.231; 3.B.244.236; 3.B.244.237; 3.B.244.238; 3.B.244.239; 3.B.244.154; 3.B.244.157; 3.B.244.166; 3.B.244.169; 3.B.244.172; 3.B.244.175; 3.B.244.240; 3.B.244.244;

Prodrugs of 3.D

3.D.228.228; 3.D.228.229; 3.D.228.230; 3.D.228.231; 3.D.228.236; 3.D.228.237; 3.D.228.238; 3.D.228.239; 3.D.228.154; 3.D.228.157; 3.D.228.166; 3.D.228.169; 3.D.228.172; 3.D.228.175; 3.D.228.240; 3.D.228.244; 3.D.229.228; 3.D.229.229;

3.D.229.230; 3.D.229.231; 3.D.229.236; 3.D.229.237; 3.D.229.238; 3.D.229.239; 3.D.229.154; 3.D.229.157; 3.D.229.166; 3.D.229.169; 3.D.229.172; 3.D.229.175; 3.D.229.240; 3.D.229.244; 3.D.230.228; 3.D.230.229; 3.D.230.230; 3.D.230.231; 3.D.230.236; 3.D.230.237; 3.D.230.238; 3.D.230.239; 3.D.230.154; 3.D.230.157; 3.D.230.166; 3.D.230.169; 3.D.230.172; 3.D.230.175; 3.D.230.240; 3.D.230.244; 3.D.231.228; 3.D.231.229; 3.D.231.230; 3.D.231.231; 3.D.231.236; 3.D.231.237; 3.D.231.238; 3.D.231.239; 3.D.231.154; 3.D.231.157; 3.D.231.166; 3.D.231.169; 3.D.231.172; 3.D.231.175; 3.D.231.240; 3.D.231.244; 3.D.236.228; 3.D.236.229; 3.D.236.230; 3.D.236.231; 3.D.236.236; 3.D.236.237; 3.D.236.238; 3.D.236.239; 3.D.236.154; 3.D.236.157; 3.D.236.166; 3.D.236.169; 3.D.236.172; 3.D.236.175; 3.D.236.240; 3.D.236.244; 3.D.237.228; 3.D.237.229; 3.D.237.230; 3.D.237.231; 3.D.237.236; 3.D.237.237; 3.D.237.238; 3.D.237.239; 3.D.237.154; 3.D.237.157; 3.D.237.166; 3.D.237.169; 3.D.237.172; 3.D.237.175; 3.D.237.240; 3.D.237.244; 3.D.238.228; 3.D.238.229; 3.D.238.230; 3.D.238.231; 3.D.238.236; 3.D.238.237; 3.D.238.238; 3.D.238.239; 3.D.238.154; 3.D.238.157; 3.D.238.166; 3.D.238.169; 3.D.238.172; 3.D.238.175; 3.D.238.240; 3.D.238.244; 3.D.239.228; 3.D.239.229; 3.D.239.230; 3.D.239.231; 3.D.239.236; 3.D.239.237; 3.D.239.238; 3.D.239.239; 3.D.239.154; 3.D.239.157; 3.D.239.166; 3.D.239.169; 3.D.239.172; 3.D.239.175; 3.D.239.240; 3.D.239.244; 3.D.154.228; 3.D.154.229; 3.D.154.230; 3.D.154.231; 3.D.154.236; 3.D.154.237; 3.D.154.238; 3.D.154.239; 3.D.154.154; 3.D.154.157; 3.D.154.166; 3.D.154.169; 3.D.154.172; 3.D.154.175; 3.D.154.240; 3.D.154.244; 3.D.157.228; 3.D.157.229; 3.D.157.230; 3.D.157.231; 3.D.157.236; 3.D.157.237; 3.D.157.238; 3.D.157.239; 3.D.157.154; 3.D.157.157; 3.D.157.166; 3.D.157.169; 3.D.157.172; 3.D.157.175; 3.D.157.240; 3.D.157.244; 3.D.166.228; 3.D.166.229; 3.D.166.230; 3.D.166.231; 3.D.166.236; 3.D.166.237; 3.D.166.238; 3.D.166.239; 3.D.166.154; 3.D.166.157; 3.D.166.166; 3.D.166.169; 3.D.166.172; 3.D.166.175; 3.D.166.240; 3.D.166.244; 3.D.169.228; 3.D.169.229; 3.D.169.230; 3.D.169.231; 3.D.169.236; 3.D.169.237; 3.D.169.238; 3.D.169.239; 3.D.169.154; 3.D.169.157; 3.D.169.166; 3.D.169.169; 3.D.169.172; 3.D.169.175; 3.D.169.240; 3.D.169.244; 3.D.172.228; 3.D.172.229; 3.D.172.230; 3.D.172.231; 3.D.172.236; 3.D.172.237; 3.D.172.238; 3.D.172.239; 3.D.172.154; 3.D.172.157; 3.D.172.166; 3.D.172.169; 3.D.172.172; 3.D.172.175; 3.D.172.240; 3.D.172.244; 3.D.175.228; 3.D.175.229; 3.D.175.230; 3.D.175.231; 3.D.175.236; 3.D.175.237; 3.D.175.238; 3.D.175.239; 3.D.175.154; 3.D.175.157; 3.D.175.166; 3.D.175.169; 3.D.175.172; 3.D.175.175; 3.D.175.240; 3.D.175.244; 3.D.240.228; 3.D.240.229; 3.D.240.230; 3.D.240.231; 3.D.240.236; 3.D.240.237; 3.D.240.238; 3.D.240.239; 3.D.240.154; 3.D.240.157; 3.D.240.166; 3.D.240.169; 3.D.240.172; 3.D.240.175; 3.D.240.240; 3.D.240.244; 3.D.244.228; 3.D.244.229; 3.D.244.230; 3.D.244.231; 3.D.244.236; 3.D.244.237; 3.D.244.238; 3.D.244.239; 3.D.244.154; 3.D.244.157; 3.D.244.166; 3.D.244.169; 3.D.244.172; 3.D.244.175; 3.D.244.240; 3.D.244.244;

<u>Prodrugs of 3.E</u>

3.E.228.228; 3.E.228.229; 3.E.228.230; 3.E.228.231; 3.E.228.236; 3.E.228.237; 3.E.228.238; 3.E.228.239; 3.E.228.154; 3.E.228.157; 3.E.228.166; 3.E.228.169; 3.E.228.172; 3.E.228.175; 3.E.228.240; 3.E.228.244; 3.E.229.228; 3.E.229.229; 3.E.229.230; 3.E.229.231; 3.E.229.236; 3.E.229.237; 3.E.229.238; 3.E.229.239; 3.E.229.154; 3.E.229.157; 3.E.229.166;

3.E.229.169; 3.E.229.172; 3.E.229.175; 3.E.229.240; 3.E.229.244; 3.E.230.228; 3.E.230.229; 3.E.230.230; 3.E.230.231; 3.E.230.236; 3.E.230.237; 3.E.230.238; 3.E.230.239; 3.E.230.154; 3.E.230.157; 3.E.230.166; 3.E.230.169; 3.E.230.172; 3.E.230.175; 3.E.230.240; 3.E.230.244; 3.E.231.228; 3.E.231.229; 3.E.231.230; 3.E.231.231; 3.E.231.236; 3.E.231.237; 3.E.231.238; 3.E.231.239; 3.E.231.154; 3.E.231.157; 3.E.231.166; 3.E.231.169; 3.E.231.172; 3.E.231.175; 3.E.231.240; 3.E.231.244; 3.E.236.228; 3.E.236.229; 3.E.236.230; 3.E.236.231; 3.E.236.236; 3.E.236.237; 3.E.236.238; 3.E.236.239; 3.E.236.154; 3.E.236.157; 3.E.236.166; 3.E.236.169; 3.E.236.172; 3.E.236.175; 3.E.236.240; 3.E.236.244; 3.E.237.228; 3.E.237.229; 3.E.237.230; 3.E.237.231; 3.E.237.236; 3.E.237.237; 3.E.237.238; 3.E.237.239; 3.E.237.154; 3.E.237.157; 3.E.237.166; 3.E.237.169; 3.E.237.172; 3.E.237.175; 3.E.237.240; 3.E.237.244; 3.E.238.228; 3.E.238.229; 3.E.238.230; 3.E.238.231; 3.E.238.236; 3.E.238.237; 3.E.238.238; 3.E.238.239; 3.E.238.154; 3.E.238.157; 3.E.238.166; 3.E.238.169; 3.E.238.172; 3.E.238.175; 3.E.238.240; 3.E.238.244; 3.E.239.228; 3.E.239.229; 3.E.239.230; 3.E.239.231; 3.E.239.236; 3.E.239.237; 3.E.239.238; 3.E.239.239; 3.E.239.154; 3.E.239.157; 3.E.239.166; 3.E.239.169; 3.E.239.172; 3.E.239.175; 3.E.239.240; 3.E.239.244; 3.E.154.228; 3.E.154.229; 3.E.154.230; 3.E.154.231; 3.E.154.236; 3.E.154.237; 3.E.154.238; 3.E.154.239; 3.E.154.154; 3.E.154.157; 3.E.154.166; 3.E.154.169; 3.E.154.172; 3.E.154.175; 3.E.154.240; 3.E.154.244; 3.E.157.228; 3.E.157.229; 3.E.157.230; 3.E.157.231; 3.E.157.236; 3.E.157.237; 3.E.157.238; 3.E.157.239; 3.E.157.154; 3.E.157.157; 3.E.157.166; 3.E.157.169; 3.E.157.172; 3.E.157.175; 3.E.157.240; 3.E.157.244; 3.E.166.228; 3.E.166.229; 3.E.166.230; 3.E.166.231; 3.E.166.236; 3.E.166.237; 3.E.166.238; 3.E.166.239; 3.E.166.154; 3.E.166.157; 3.E.166.166; 3.E.166.169; 3.E.166.172; 3.E.166.175; 3.E.166.240; 3.E.166.244; 3.E.169.228; 3.E.169.229; 3.E.169.230; 3.E.169.231; 3.E.169.236; 3.E.169.237; 3.E.169.238; 3.E.169.239; 3.E.169.154; 3.E.169.157; 3.E.169.166; 3.E.169.169; 3.E.169.172; 3.E.169.175; 3.E.169.240; 3.E.169.244; 3.E.172.228; 3.E.172.229; 3.E.172.230; 3.E.172.231; 3.E.172.236; 3.E.172.237; 3.E.172.238; 3.E.172.239; 3.E.172.154; 3.E.172.157; 3.E.172.166; 3.E.172.169; 3.E.172.172; 3.E.172.175; 3.E.172.240; 3.E.172.244; 3.E.175.228; 3.E.175.229; 3.E.175.230; 3.E.175.231; 3.E.175.236; 3.E.175.237; 3.E.175.238; 3.E.175.239; 3.E.175.154; 3.E.175.157; 3.E.175.166; 3.E.175.169; 3.E.175.172; 3.E.175.175; 3.E.175.240; 3.E.175.244; 3.E.240.228; 3.E.240.229; 3.E.240.230; 3.E.240.231; 3.E.240.236; 3.E.240.237; 3.E.240.238; 3.E.240.239; 3.E.240.154; 3.E.240.157; 3.E.240.166; 3.E.240.169; 3.E.240.172; 3.E.240.175; 3.E.240.240; 3.E.240.244; 3.E.244.228; 3.E.244.229; 3.E.244.230; 3.E.244.231; 3.E.244.236; 3.E.244.237; 3.E.244.238; 3.E.244.239; 3.E.244.154; 3.E.244.157; 3.E.244.166; 3.E.244.169; 3.E.244.172; 3.E.244.175; 3.E.244.240; 3.E.244.244;

Prodrugs of 3.G

3.G.228.228; 3.G.228.229; 3.G.228.230; 3.G.228.231; 3.G.228.236; 3.G.228.237; 3.G.228.238; 3.G.228.239; 3.G.228.154; 3.G.228.157; 3.G.228.166; 3.G.228.169; 3.G.228.172; 3.G.228.175; 3.G.228.240; 3.G.228.244; 3.G.229.228; 3.G.229.229; 3.G.229.230; 3.G.229.231; 3.G.229.236; 3.G.229.237; 3.G.229.238; 3.G.229.239; 3.G.229.154; 3.G.229.157; 3.G.229.166; 3.G.229.169; 3.G.229.172; 3.G.229.175; 3.G.229.240; 3.G.229.244; 3.G.230.228; 3.G.230.229; 3.G.230.230; 3.G.230.231; 3.G.230.236; 3.G.230.237; 3.G.230.238; 3.G.230.239; 3.G.230.154; 3.G.230.157; 3.G.230.166; 3.G.230.169; 3.G.230.172; 3.G.230.175; 3.G.230.240; 3.G.230.244; 3.G.231.228; 3.G.231.229; 3.G.231.230; 3.G.231.231; 3.G.231.236; 3.G.231.237; 3.G.231.238; 3.G.231.239; 3.G.231.154; 3.G.231.157; 3.G.231.166; 3.G.231.169; 3.G.231.172; 3.G.231.175; 3.G.231.240; 3.G.231.244; 3.G.236.228; 3.G.236.229;

3.G.236.230; 3.G.236.231; 3.G.236.236; 3.G.236.237; 3.G.236.238; 3.G.236.239; 3.G.236.154; 3.G.236.157; 3.G.236.166; 3.G.236.169; 3.G.236.172; 3.G.236.175; 3.G.236.240; 3.G.236.244; 3.G.237.228; 3.G.237.229; 3.G.237.230; 3.G.237.231; 3.G.237.236; 3.G.237.237; 3.G.237.238; 3.G.237.239; 3.G.237.154; 3.G.237.157; 3.G.237.166; 3.G.237.169; 3.G.237.172; 3.G.237.175; 3.G.237.240; 3.G.237.244; 3.G.238.228; 3.G.238.229; 3.G.238.230; 3.G.238.231; 3.G.238.236; 3.G.238.237; 3.G.238.238; 3.G.238.239; 3.G.238.154; 3.G.238.157; 3.G.238.166; 3.G.238.169; 3.G.238.172; 3.G.238.175; 3.G.238.240; 3.G.238.244; 3.G.239.228; 3.G.239.229; 3.G.239.230; 3.G.239.231; 3.G.239.236; 3.G.239.237; 3.G.239.238; 3.G.239.239; 3.G.239.154; 3.G.239.157; 3.G.239.166; 3.G.239.169; 3.G.239.172; 3.G.239.175; 3.G.239.240; 3.G.239.244; 3.G.154.228; 3.G.154.229; 3.G.154.230; 3.G.154.231; 3.G.154.236; 3.G.154.237; 3.G.154.238; 3.G.154.239; 3.G.154.154; 3.G.154.157; 3.G.154.166; 3.G.154.169; 3.G.154.172; 3.G.154.175; 3.G.154.240; 3.G.154.244; 3.G.157.228; 3.G.157.229; 3.G.157.230; 3.G.157.231; 3.G.157.236; 3.G.157.237; 3.G.157.238; 3.G.157.239; 3.G.157.154; 3.G.157.157; 3.G.157.166; 3.G.157.169; 3.G.157.172; 3.G.157.175; 3.G.157.240; 3.G.157.244; 3.G.166.228; 3.G.166.229; 3.G.166.230; 3.G.166.231; 3.G.166.236; 3.G.166.237; 3.G.166.238; 3.G.166.239; 3.G.166.154; 3.G.166.157; 3.G.166.166; 3.G.166.169; 3.G.166.172; 3.G.166.175; 3.G.166.240; 3.G.166.244; 3.G.169.228; 3.G.169.229; 3.G.169.230; 3.G.169.231; 3.G.169.236; 3.G.169.237; 3.G.169.238; 3.G.169.239; 3.G.169.154; 3.G.169.157; 3.G.169.166; 3.G.169.169; 3.G.169.172; 3.G.169.175; 3.G.169.240; 3.G.169.244; 3.G.172.228; 3.G.172.229; 3.G.172.230; 3.G.172.231; 3.G.172.236; 3.G.172.237; 3.G.172.238; 3.G.172.239; 3.G.172.154; 3.G.172.157; 3.G.172.166; 3.G.172.169; 3.G.172.172; 3.G.172.175; 3.G.172.240; 3.G.172.244; 3.G.175.228; 3.G.175.229; 3.G.175.230; 3.G.175.231; 3.G.175.236; 3.G.175.237; 3.G.175.238; 3.G.175.239; 3.G.175.154; 3.G.175.157; 3.G.175.166; 3.G.175.169; 3.G.175.172; 3.G.175.175; 3.G.175.240; 3.G.175.244; 3.G.240.228; 3.G.240.229; 3.G.240.230; 3.G.240.231; 3.G.240.236; 3.G.240.237; 3.G.240.238; 3.G.240.239; 3.G.240.154; 3.G.240.157; 3.G.240.166; 3.G.240.169; 3.G.240.172; 3.G.240.175; 3.G.240.240; 3.G.240.244; 3.G.244.228; 3.G.244.229; 3.G.244.230; 3.G.244.231; 3.G.244.236; 3.G.244.237; 3.G.244.238; 3.G.244.239; 3.G.244.154; 3.G.244.157; 3.G.244.166; 3.G.244.169; 3.G.244.172; 3.G.244.175; 3.G.244.240; 3.G.244.244;

Prodrugs of 3.I

3.I.228.228; 3.I.228.229; 3.I.228.230; 3.I.228.231; 3.I.228.236; 3.I.228.237; 3.I.228.238; 3.I.228.239; 3.I.228.154; 3.I.228.157; 3.I.228.166; 3.I.228.169; 3.I.228.172; 3.I.228.175; 3.I.228.240; 3.I.228.244; 3.I.229.228; 3.I.229.229; 3.I.229.230; 3.I.229.231; 3.I.229.236; 3.I.229.237; 3.I.229.238; 3.I.229.239; 3.I.229.154; 3.I.229.157; 3.I.229.166; 3.I.229.169; 3.I.229.172; 3.I.229.175; 3.I.229.240; 3.I.229.244; 3.I.230.228; 3.I.230.229; 3.I.230.230; 3.I.230.231; 3.I.230.236; 3.I.230.237; 3.I.230.238; 3.I.230.239; 3.I.230.154; 3.I.230.157; 3.I.230.166; 3.I.230.169; 3.I.230.172; 3.I.230.175; 3.I.230.240; 3.I.230.244; 3.I.231.228; 3.I.231.229; 3.I.231.230; 3.I.231.231; 3.I.231.236; 3.I.231.237; 3.I.231.238; 3.I.231.239; 3.I.231.154; 3.I.231.157; 3.I.231.166; 3.I.231.169; 3.I.231.172; 3.I.231.175; 3.I.231.240; 3.I.231.244; 3.I.236.228; 3.I.236.229; 3.I.236.230; 3.I.236.231; 3.I.236.236; 3.I.236.237; 3.I.236.238; 3.I.236.239; 3.I.236.154; 3.I.236.157; 3.I.236.166; 3.I.236.169; 3.I.236.172; 3.I.236.175; 3.I.236.240; 3.I.236.244; 3.I.237.228; 3.I.237.229; 3.I.237.230; 3.I.237.231;

3.I.237.236; 3.I.237.237; 3.I.237.238; 3.I.237.239; 3.I.237.154; 3.I.237.157; 3.I.237.166; 3.I.237.169; 3.I.237.172; 3.I.237.175; 3.I.237.240; 3.I.237.244; 3.I.238.228; 3.I.238.229; 3.I.238.230; 3.I.238.231; 3.I.238.236; 3.I.238.237; 3.I.238.238; 3.I.238.239; 3.I.238.154; 3.I.238.157; 3.I.238.166; 3.I.238.169; 3.I.238.172; 3.I.238.175; 3.I.238.240; 3.I.238.244; 3.I.239.228; 3.I.239.229; 3.I.239.230; 3.I.239.231; 3.I.239.236; 3.I.239.237; 3.I.239.238; 3.I.239.239; 3.I.239.154; 3.I.239.157; 3.I.239.166; 3.I.239.169; 3.I.239.172; 3.I.239.175; 3.I.239.240; 3.I.239.244; 3.I.154.228; 3.I.154.229; 3.I.154.230; 3.I.154.231; 3.I.154.236; 3.I.154.237; 3.I.154.238; 3.I.154.239; 3.I.154.154; 3.I.154.157; 3.I.154.166; 3.I.154.169; 3.I.154.172; 3.I.154.175; 3.I.154.240; 3.I.154.244; 3.I.157.228; 3.I.157.229; 3.I.157.230; 3.I.157.231; 3.I.157.236; 3.I.157.237; 3.I.157.238; 3.I.157.239; 3.I.157.154; 3.I.157.157; 3.I.157.166; 3.I.157.169; 3.I.157.172; 3.I.157.175; 3.I.157.240; 3.I.157.244; 3.I.166.228; 3.I.166.229; 3.I.166.230; 3.I.166.231; 3.I.166.236; 3.I.166.237; 3.I.166.238; 3.I.166.239; 3.I.166.154; 3.I.166.157; 3.I.166.166; 3.I.166.169; 3.I.166.172; 3.I.166.175; 3.I.166.240; 3.I.166.244; 3.I.169.228; 3.I.169.229; 3.I.169.230; 3.I.169.231; 3.I.169.236; 3.I.169.237; 3.I.169.238; 3.I.169.239; 3.I.169.154; 3.I.169.157; 3.I.169.166; 3.I.169.169; 3.I.169.172; 3.I.169.175; 3.I.169.240; 3.I.169.244; 3.I.172.228; 3.I.172.229; 3.I.172.230; 3.I.172.231; 3.I.172.236; 3.I.172.237; 3.I.172.238; 3.I.172.239; 3.I.172.154; 3.I.172.157; 3.I.172.166; 3.I.172.169; 3.I.172.172; 3.I.172.175; 3.I.172.240; 3.I.172.244; 3.I.175.228; 3.I.175.229; 3.I.175.230; 3.I.175.231; 3.I.175.236; 3.I.175.237; 3.I.175.238; 3.I.175.239; 3.I.175.154; 3.I.175.157; 3.I.175.166; 3.I.175.169; 3.I.175.172; 3.I.175.175; 3.I.175.240; 3.I.175.244; 3.I.240.228; 3.I.240.229; 3.I.240.230; 3.I.240.231; 3.I.240.236; 3.I.240.237; 3.I.240.238; 3.I.240.239; 3.I.240.154; 3.I.240.157; 3.I.240.166; 3.I.240.169; 3.I.240.172; 3.I.240.175; 3.I.240.240; 3.I.240.244; 3.I.244.228; 3.I.244.229; 3.I.244.230; 3.I.244.231; 3.I.244.236; 3.I.244.237; 3.I.244.238; 3.I.244.239; 3.I.244.154; 3.I.244.157; 3.I.244.166; 3.I.244.169; 3.I.244.172; 3.I.244.175; 3.I.244.240; 3.I.244.244;

Prodrugs of 3.J

3.J.228.228; 3.J.228.229; 3.J.228.230; 3.J.228.231; 3.J.228.236; 3.J.228.237; 3.J.228.238; 3.J.228.239; 3.J.228.154; 3.J.228.157; 3.J.228.166; 3.J.228.169; 3.J.228.172; 3.J.228.175; 3.J.228.240; 3.J.228.244; 3.J.229.228; 3.J.229.229; 3.J.229.230; 3.J.229.231; 3.J.229.236; 3.J.229.237; 3.J.229.238; 3.J.229.239; 3.J.229.154; 3.J.229.157; 3.J.229.166; 3.J.229.169; 3.J.229.172; 3.J.229.175; 3.J.229.240; 3.J.229.244; 3.J.230.228; 3.J.230.229; 3.J.230.230; 3.J.230.231; 3.J.230.236; 3.J.230.237; 3.J.230.238; 3.J.230.239; 3.J.230.154; 3.J.230.157; 3.J.230.166; 3.J.230.169; 3.J.230.172; 3.J.230.175; 3.J.230.240; 3.J.230.244; 3.J.231.228; 3.J.231.229; 3.J.231.230; 3.J.231.231; 3.J.231.236; 3.J.231.237; 3.J.231.238; 3.J.231.239; 3.J.231.154; 3.J.231.157; 3.J.231.166; 3.J.231.169; 3.J.231.172; 3.J.231.175; 3.J.231.240; 3.J.231.244; 3.J.236.228; 3.J.236.229; 3.J.236.230; 3.J.236.231; 3.J.236.236; 3.J.236.237; 3.J.236.238; 3.J.236.239; 3.J.236.154; 3.J.236.157; 3.J.236.166; 3.J.236.169; 3.J.236.172; 3.J.236.175; 3.J.236.240; 3.J.236.244; 3.J.237.228; 3.J.237.229; 3.J.237.230; 3.J.237.231; 3.J.237.236; 3.J.237.237; 3.J.237.238; 3.J.237.239; 3.J.237.154; 3.J.237.157; 3.J.237.166; 3.J.237.169; 3.J.237.172; 3.J.237.175; 3.J.237.240; 3.J.237.244; 3.J.238.228; 3.J.238.229; 3.J.238.230; 3.J.238.231; 3.J.238.236; 3.J.238.237; 3.J.238.238; 3.J.238.239; 3.J.238.154; 3.J.238.157; 3.J.238.166; 3.J.238.169; 3.J.238.172; 3.J.238.175; 3.J.238.240; 3.J.238.244; 3.J.239.228; 3.J.239.229; 3.J.239.230; 3.J.239.231; 3.J.239.236; 3.J.239.237; 3.J.239.238; 3.J.239.239; 3.J.239.154; 3.J.239.157; 3.J.239.166; 3.J.239.169; 3.J.239.172; 3.J.239.175; 3.J.239.240; 3.J.239.244; 3.J.154.228; 3.J.154.229; 3.J.154.230; 3.J.154.231; 3.J.154.236;

3.J.154.237; 3.J.154.238; 3.J.154.239; 3.J.154.154; 3.J.154.157; 3.J.154.166; 3.J.154.169; 3.J.154.172; 3.J.154.175; 3.J.154.240; 3.J.154.244; 3.J.157.228; 3.J.157.229; 3.J.157.230; 3.J.157.231; 3.J.157.236; 3.J.157.237; 3.J.157.238; 3.J.157.239; 3.J.157.154; 3.J.157.157; 3.J.157.166; 3.J.157.169; 3.J.157.172; 3.J.157.175; 3.J.157.240; 3.J.157.244; 3.J.166.228; 3.J.166.229; 3.J.166.230; 3.J.166.231; 3.J.166.236; 3.J.166.237; 3.J.166.238; 3.J.166.239; 3.J.166.154; 3.J.166.157; 3.J.166.166; 3.J.166.169; 3.J.166.172; 3.J.166.175; 3.J.166.240; 3.J.166.244; 3.J.169.228; 3.J.169.229; 3.J.169.230; 3.J.169.231; 3.J.169.236; 3.J.169.237; 3.J.169.238; 3.J.169.239; 3.J.169.154; 3.J.169.157; 3.J.169.166; 3.J.169.169; 3.J.169.172; 3.J.169.175; 3.J.169.240; 3.J.169.244; 3.J.172.228; 3.J.172.229; 3.J.172.230; 3.J.172.231; 3.J.172.236; 3.J.172.237; 3.J.172.238; 3.J.172.239; 3.J.172.154; 3.J.172.157; 3.J.172.166; 3.J.172.169; 3.J.172.172; 3.J.172.175; 3.J.172.240; 3.J.172.244; 3.J.175.228; 3.J.175.229; 3.J.175.230; 3.J.175.231; 3.J.175.236; 3.J.175.237; 3.J.175.238; 3.J.175.239; 3.J.175.154; 3.J.175.157; 3.J.175.166; 3.J.175.169; 3.J.175.172; 3.J.175.175; 3.J.175.240; 3.J.175.244; 3.J.240.228; 3.J.240.229; 3.J.240.230; 3.J.240.231; 3.J.240.236; 3.J.240.237; 3.J.240.238; 3.J.240.239; 3.J.240.154; 3.J.240.157; 3.J.240.166; 3.J.240.169; 3.J.240.172; 3.J.240.175; 3.J.240.240; 3.J.240.244; 3.J.244.228; 3.J.244.229; 3.J.244.230; 3.J.244.231; 3.J.244.236; 3.J.244.237; 3.J.244.238; 3.J.244.239; 3.J.244.154; 3.J.244.157; 3.J.244.166; 3.J.244.169; 3.J.244.172; 3.J.244.175; 3.J.244.240; 3.J.244.244;

Prodrugs of 3.L

3.L.228.228; 3.L.228.229; 3.L.228.230; 3.L.228.231; 3.L.228.236; 3.L.228.237; 3.L.228.238; 3.L.228.239; 3.L.228.154; 3.L.228.157; 3.L.228.166; 3.L.228.169; 3.L.228.172; 3.L.228.175; 3.L.228.240; 3.L.228.244; 3.L.229.228; 3.L.229.229; 3.L.229.230; 3.L.229.231; 3.L.229.236; 3.L.229.237; 3.L.229.238; 3.L.229.239; 3.L.229.154; 3.L.229.157; 3.L.229.166; 3.L.229.169; 3.L.229.172; 3.L.229.175; 3.L.229.240; 3.L.229.244; 3.L.230.228; 3.L.230.229; 3.L.230.230; 3.L.230.231; 3.L.230.236; 3.L.230.237; 3.L.230.238; 3.L.230.239; 3.L.230.154; 3.L.230.157; 3.L.230.166; 3.L.230.169; 3.L.230.172; 3.L.230.175; 3.L.230.240; 3.L.230.244; 3.L.231.228; 3.L.231.229; 3.L.231.230; 3.L.231.231; 3.L.231.236; 3.L.231.237; 3.L.231.238; 3.L.231.239; 3.L.231.154; 3.L.231.157; 3.L.231.166; 3.L.231.169; 3.L.231.172; 3.L.231.175; 3.L.231.240; 3.L.231.244; 3.L.236.228; 3.L.236.229; 3.L.236.230; 3.L.236.231; 3.L.236.236; 3.L.236.237; 3.L.236.238; 3.L.236.239; 3.L.236.154; 3.L.236.157; 3.L.236.166; 3.L.236.169; 3.L.236.172; 3.L.236.175; 3.L.236.240; 3.L.236.244; 3.L.237.228; 3.L.237.229; 3.L.237.230; 3.L.237.231; 3.L.237.236; 3.L.237.237; 3.L.237.238; 3.L.237.239; 3.L.237.154; 3.L.237.157; 3.L.237.166; 3.L.237.169; 3.L.237.172; 3.L.237.175; 3.L.237.240; 3.L.237.244; 3.L.238.228; 3.L.238.229; 3.L.238.230; 3.L.238.231; 3.L.238.236; 3.L.238.237; 3.L.238.238; 3.L.238.239; 3.L.238.154; 3.L.238.157; 3.L.238.166; 3.L.238.169; 3.L.238.172; 3.L.238.175; 3.L.238.240; 3.L.238.244; 3.L.239.228; 3.L.239.229; 3.L.239.230; 3.L.239.231; 3.L.239.236; 3.L.239.237; 3.L.239.238; 3.L.239.239; 3.L.239.154; 3.L.239.157; 3.L.239.166; 3.L.239.169; 3.L.239.172; 3.L.239.175; 3.L.239.240; 3.L.239.244; 3.L.154.228; 3.L.154.229; 3.L.154.230; 3.L.154.231; 3.L.154.236; 3.L.154.237; 3.L.154.238; 3.L.154.239; 3.L.154.154; 3.L.154.157; 3.L.154.166; 3.L.154.169; 3.L.154.172; 3.L.154.175; 3.L.154.240; 3.L.154.244; 3.L.157.228; 3.L.157.229; 3.L.157.230; 3.L.157.231; 3.L.157.236; 3.L.157.237; 3.L.157.238; 3.L.157.239; 3.L.157.154; 3.L.157.157; 3.L.157.166; 3.L.157.169; 3.L.157.172; 3.L.157.175; 3.L.157.240; 3.L.157.244; 3.L.166.228; 3.L.166.229; 3.L.166.230; 3.L.166.231; 3.L.166.236; 3.L.166.237; 3.L.166.238; 3.L.166.239; 3.L.166.154; 3.L.166.157; 3.L.166.166; 3.L.166.169; 3.L.166.172; 3.L.166.175; 3.L.166.240; 3.L.166.244; 3.L.169.228; 3.L.169.229; 3.L.169.230; 3.L.169.231; 3.L.169.236;

3.L.169.237; 3.L.169.238; 3.L.169.239; 3.L.169.154; 3.L.169.157; 3.L.169.166; 3.L.169.169; 3.L.169.172; 3.L.169.175; 3.L.169.240; 3.L.169.244; 3.L.172.228; 3.L.172.229; 3.L.172.230; 3.L.172.231; 3.L.172.236; 3.L.172.237; 3.L.172.238; 3.L.172.239; 3.L.172.154; 3.L.172.157; 3.L.172.166; 3.L.172.169; 3.L.172.172; 3.L.172.175; 3.L.172.240; 3.L.172.244; 3.L.175.228; 3.L.175.229; 3.L.175.230; 3.L.175.231; 3.L.175.236; 3.L.175.237; 3.L.175.238; 3.L.175.239; 3.L.175.154; 3.L.175.157; 3.L.175.166; 3.L.175.169; 3.L.175.172; 3.L.175.175; 3.L.175.240; 3.L.175.244; 3.L.240.228; 3.L.240.229; 3.L.240.230; 3.L.240.231; 3.L.240.236; 3.L.240.237; 3.L.240.238; 3.L.240.239; 3.L.240.154; 3.L.240.157; 3.L.240.166; 3.L.240.169; 3.L.240.172; 3.L.240.175; 3.L.240.240; 3.L.240.244; 3.L.244.228; 3.L.244.229; 3.L.244.230; 3.L.244.231; 3.L.244.236; 3.L.244.237; 3.L.244.238; 3.L.244.239; 3.L.244.154; 3.L.244.157; 3.L.244.166; 3.L.244.169; 3.L.244.172; 3.L.244.175; 3.L.244.240; 3.L.244.244;

Prodrugs of 3.O

3.O.228.228; 3.O.228.229; 3.O.228.230; 3.O.228.231; 3.O.228.236; 3.O.228.237; 3.O.228.238; 3.O.228.239; 3.O.228.154; 3.O.228.157; 3.O.228.166; 3.O.228.169; 3.O.228.172; 3.O.228.175; 3.O.228.240; 3.O.228.244; 3.O.229.228; 3.O.229.229; 3.O.229.230; 3.O.229.231; 3.O.229.236; 3.O.229.237; 3.O.229.238; 3.O.229.239; 3.O.229.154; 3.O.229.157; 3.O.229.166; 3.O.229.169; 3.O.229.172; 3.O.229.175; 3.O.229.240; 3.O.229.244; 3.O.230.228; 3.O.230.229; 3.O.230.230; 3.O.230.231; 3.O.230.236; 3.O.230.237; 3.O.230.238; 3.O.230.239; 3.O.230.154; 3.O.230.157; 3.O.230.166; 3.O.230.169; 3.O.230.172; 3.O.230.175; 3.O.230.240; 3.O.230.244; 3.O.231.228; 3.O.231.229; 3.O.231.230; 3.O.231.231; 3.O.231.236; 3.O.231.237; 3.O.231.238; 3.O.231.239; 3.O.231.154; 3.O.231.157; 3.O.231.166; 3.O.231.169; 3.O.231.172; 3.O.231.175; 3.O.231.240; 3.O.231.244; 3.O.236.228; 3.O.236.229; 3.O.236.230; 3.O.236.231; 3.O.236.236; 3.O.236.237; 3.O.236.238; 3.O.236.239; 3.O.236.154; 3.O.236.157; 3.O.236.166; 3.O.236.169; 3.O.236.172; 3.O.236.175; 3.O.236.240; 3.O.236.244; 3.O.237.228; 3.O.237.229; 3.O.237.230; 3.O.237.231; 3.O.237.236; 3.O.237.237; 3.O.237.238; 3.O.237.239; 3.O.237.154; 3.O.237.157; 3.O.237.166; 3.O.237.169; 3.O.237.172; 3.O.237.175; 3.O.237.240; 3.O.237.244; 3.O.238.228; 3.O.238.229; 3.O.238.230; 3.O.238.231; 3.O.238.236; 3.O.238.237; 3.O.238.238; 3.O.238.239; 3.O.238.154; 3.O.238.157; 3.O.238.166; 3.O.238.169; 3.O.238.172; 3.O.238.175; 3.O.238.240; 3.O.238.244; 3.O.239.228; 3.O.239.229; 3.O.239.230; 3.O.239.231; 3.O.239.236; 3.O.239.237; 3.O.239.238; 3.O.239.239; 3.O.239.154; 3.O.239.157; 3.O.239.166; 3.O.239.169; 3.O.239.172; 3.O.239.175; 3.O.239.240; 3.O.239.244; 3.O.154.228; 3.O.154.229; 3.O.154.230; 3.O.154.231; 3.O.154.236; 3.O.154.237; 3.O.154.238; 3.O.154.239; 3.O.154.154; 3.O.154.157; 3.O.154.166; 3.O.154.169; 3.O.154.172; 3.O.154.175; 3.O.154.240; 3.O.154.244; 3.O.157.228; 3.O.157.229; 3.O.157.230; 3.O.157.231; 3.O.157.236; 3.O.157.237; 3.O.157.238; 3.O.157.239; 3.O.157.154; 3.O.157.157; 3.O.157.166; 3.O.157.169; 3.O.157.172; 3.O.157.175; 3.O.157.240; 3.O.157.244; 3.O.166.228; 3.O.166.229; 3.O.166.230; 3.O.166.231; 3.O.166.236; 3.O.166.237; 3.O.166.238; 3.O.166.239; 3.O.166.154; 3.O.166.157; 3.O.166.166; 3.O.166.169; 3.O.166.172; 3.O.166.175; 3.O.166.240; 3.O.166.244; 3.O.169.228; 3.O.169.229; 3.O.169.230; 3.O.169.231; 3.O.169.236; 3.O.169.237; 3.O.169.238; 3.O.169.239; 3.O.169.154; 3.O.169.157; 3.O.169.166; 3.O.169.169; 3.O.169.172; 3.O.169.175; 3.O.169.240; 3.O.169.244; 3.O.172.228; 3.O.172.229; 3.O.172.230; 3.O.172.231; 3.O.172.236; 3.O.172.237;

3.O.172.238; 3.O.172.239; 3.O.172.154; 3.O.172.157; 3.O.172.166; 3.O.172.169; 3.O.172.172; 3.O.172.175; 3.O.172.240; 3.O.172.244; 3.O.175.228; 3.O.175.229; 3.O.175.230; 3.O.175.231; 3.O.175.236; 3.O.175.237; 3.O.175.238; 3.O.175.239; 3.O.175.154; 3.O.175.157; 3.O.175.166; 3.O.175.169; 3.O.175.172; 3.O.175.175; 3.O.175.240; 3.O.175.244; 3.O.240.228; 3.O.240.229; 3.O.240.230; 3.O.240.231; 3.O.240.236; 3.O.240.237; 3.O.240.238; 3.O.240.239; 3.O.240.154; 3.O.240.157; 3.O.240.166; 3.O.240.169; 3.O.240.172; 3.O.240.175; 3.O.240.240; 3.O.240.244; 3.O.244.228; 3.O.244.229; 3.O.244.230; 3.O.244.231; 3.O.244.236; 3.O.244.237; 3.O.244.238; 3.O.244.239; 3.O.244.154; 3.O.244.157; 3.O.244.166; 3.O.244.169; 3.O.244.172; 3.O.244.175; 3.O.244.240; 3.O.244.244;

Prodrugs of 3.P

3.P.228.228; 3.P.228.229; 3.P.228.230; 3.P.228.231; 3.P.228.236; 3.P.228.237; 3.P.228.238; 3.P.228.239; 3.P.228.154; 3.P.228.157; 3.P.228.166; 3.P.228.169; 3.P.228.172; 3.P.228.175; 3.P.228.240; 3.P.228.244; 3.P.229.228; 3.P.229.229; 3.P.229.230; 3.P.229.231; 3.P.229.236; 3.P.229.237; 3.P.229.238; 3.P.229.239; 3.P.229.154; 3.P.229.157; 3.P.229.166; 3.P.229.169; 3.P.229.172; 3.P.229.175; 3.P.229.240; 3.P.229.244; 3.P.230.228; 3.P.230.229; 3.P.230.230; 3.P.230.231; 3.P.230.236; 3.P.230.237; 3.P.230.238; 3.P.230.239; 3.P.230.154; 3.P.230.157; 3.P.230.166; 3.P.230.169; 3.P.230.172; 3.P.230.175; 3.P.230.240; 3.P.230.244; 3.P.231.228; 3.P.231.229; 3.P.231.230; 3.P.231.231; 3.P.231.236; 3.P.231.237; 3.P.231.238; 3.P.231.239; 3.P.231.154; 3.P.231.157; 3.P.231.166; 3.P.231.169; 3.P.231.172; 3.P.231.175; 3.P.231.240; 3.P.231.244; 3.P.236.228; 3.P.236.229; 3.P.236.230; 3.P.236.231; 3.P.236.236; 3.P.236.237; 3.P.236.238; 3.P.236.239; 3.P.236.154; 3.P.236.157; 3.P.236.166; 3.P.236.169; 3.P.236.172; 3.P.236.175; 3.P.236.240; 3.P.236.244; 3.P.237.228; 3.P.237.229; 3.P.237.230; 3.P.237.231; 3.P.237.236; 3.P.237.237; 3.P.237.238; 3.P.237.239; 3.P.237.154; 3.P.237.157; 3.P.237.166; 3.P.237.169; 3.P.237.172; 3.P.237.175; 3.P.237.240; 3.P.237.244; 3.P.238.228; 3.P.238.229; 3.P.238.230; 3.P.238.231; 3.P.238.236; 3.P.238.237; 3.P.238.238; 3.P.238.239; 3.P.238.154; 3.P.238.157; 3.P.238.166; 3.P.238.169; 3.P.238.172; 3.P.238.175; 3.P.238.240; 3.P.238.244; 3.P.239.228; 3.P.239.229; 3.P.239.230; 3.P.239.231; 3.P.239.236; 3.P.239.237; 3.P.239.238; 3.P.239.239; 3.P.239.154; 3.P.239.157; 3.P.239.166; 3.P.239.169; 3.P.239.172; 3.P.239.175; 3.P.239.240; 3.P.239.244; 3.P.154.228; 3.P.154.229; 3.P.154.230; 3.P.154.231; 3.P.154.236; 3.P.154.237; 3.P.154.238; 3.P.154.239; 3.P.154.154; 3.P.154.157; 3.P.154.166; 3.P.154.169; 3.P.154.172; 3.P.154.175; 3.P.154.240; 3.P.154.244; 3.P.157.228; 3.P.157.229; 3.P.157.230; 3.P.157.231; 3.P.157.236; 3.P.157.237; 3.P.157.238; 3.P.157.239; 3.P.157.154; 3.P.157.157; 3.P.157.166; 3.P.157.169; 3.P.157.172; 3.P.157.175; 3.P.157.240; 3.P.157.244; 3.P.166.228; 3.P.166.229; 3.P.166.230; 3.P.166.231; 3.P.166.236; 3.P.166.237; 3.P.166.238; 3.P.166.239; 3.P.166.154; 3.P.166.157; 3.P.166.166; 3.P.166.169; 3.P.166.172; 3.P.166.175; 3.P.166.240; 3.P.166.244; 3.P.169.228; 3.P.169.229; 3.P.169.230; 3.P.169.231; 3.P.169.236; 3.P.169.237; 3.P.169.238; 3.P.169.239; 3.P.169.154; 3.P.169.157; 3.P.169.166; 3.P.169.169; 3.P.169.172; 3.P.169.175; 3.P.169.240; 3.P.169.244; 3.P.172.228; 3.P.172.229; 3.P.172.230; 3.P.172.231; 3.P.172.236; 3.P.172.237; 3.P.172.238; 3.P.172.239; 3.P.172.154; 3.P.172.157; 3.P.172.166; 3.P.172.169; 3.P.172.172; 3.P.172.175; 3.P.172.240; 3.P.172.244; 3.P.175.228; 3.P.175.229; 3.P.175.230; 3.P.175.231; 3.P.175.236; 3.P.175.237; 3.P.175.238; 3.P.175.239; 3.P.175.154; 3.P.175.157; 3.P.175.166; 3.P.175.169; 3.P.175.172; 3.P.175.175; 3.P.175.240; 3.P.175.244; 3.P.240.228; 3.P.240.229; 3.P.240.230; 3.P.240.231; 3.P.240.236; 3.P.240.237; 3.P.240.238; 3.P.240.239; 3.P.240.154; 3.P.240.157; 3.P.240.166; 3.P.240.169; 3.P.240.172;

3.P.240.175; 3.P.240.240; 3.P.240.244; 3.P.244.228; 3.P.244.229; 3.P.244.230; 3.P.244.231; 3.P.244.236; 3.P.244.237; 3.P.244.238; 3.P.244.239; 3.P.244.154; 3.P.244.157; 3.P.244.166; 3.P.244.169; 3.P.244.172; 3.P.244.175; 3.P.244.240; 3.P.244.244;

Prodrugs of 3.U

3.U.228.228; 3.U.228.229; 3.U.228.230; 3.U.228.231; 3.U.228.236; 3.U.228.237; 3.U.228.238; 3.U.228.239; 3.U.228.154; 3.U.228.157; 3.U.228.166; 3.U.228.169; 3.U.228.172; 3.U.228.175; 3.U.228.240; 3.U.228.244; 3.U.229.228; 3.U.229.229; 3.U.229.230; 3.U.229.231; 3.U.229.236; 3.U.229.237; 3.U.229.238; 3.U.229.239; 3.U.229.154; 3.U.229.157; 3.U.229.166; 3.U.229.169; 3.U.229.172; 3.U.229.175; 3.U.229.240; 3.U.229.244; 3.U.230.228; 3.U.230.229; 3.U.230.230; 3.U.230.231; 3.U.230.236; 3.U.230.237; 3.U.230.238; 3.U.230.239; 3.U.230.154; 3.U.230.157; 3.U.230.166; 3.U.230.169; 3.U.230.172; 3.U.230.175; 3.U.230.240; 3.U.230.244; 3.U.231.228; 3.U.231.229; 3.U.231.230; 3.U.231.231; 3.U.231.236; 3.U.231.237; 3.U.231.238; 3.U.231.239; 3.U.231.154; 3.U.231.157; 3.U.231.166; 3.U.231.169; 3.U.231.172; 3.U.231.175; 3.U.231.240; 3.U.231.244; 3.U.236.228; 3.U.236.229; 3.U.236.230; 3.U.236.231; 3.U.236.236; 3.U.236.237; 3.U.236.238; 3.U.236.239; 3.U.236.154; 3.U.236.157; 3.U.236.166; 3.U.236.169; 3.U.236.172; 3.U.236.175; 3.U.236.240; 3.U.236.244; 3.U.237.228; 3.U.237.229; 3.U.237.230; 3.U.237.231; 3.U.237.236; 3.U.237.237; 3.U.237.238; 3.U.237.239; 3.U.237.154; 3.U.237.157; 3.U.237.166; 3.U.237.169; 3.U.237.172; 3.U.237.175; 3.U.237.240; 3.U.237.244; 3.U.238.228; 3.U.238.229; 3.U.238.230; 3.U.238.231; 3.U.238.236; 3.U.238.237; 3.U.238.238; 3.U.238.239; 3.U.238.154; 3.U.238.157; 3.U.238.166; 3.U.238.169; 3.U.238.172; 3.U.238.175; 3.U.238.240; 3.U.238.244; 3.U.239.228; 3.U.239.229; 3.U.239.230; 3.U.239.231; 3.U.239.236; 3.U.239.237; 3.U.239.238; 3.U.239.239; 3.U.239.154; 3.U.239.157; 3.U.239.166; 3.U.239.169; 3.U.239.172; 3.U.239.175; 3.U.239.240; 3.U.239.244; 3.U.154.228; 3.U.154.229; 3.U.154.230; 3.U.154.231; 3.U.154.236; 3.U.154.237; 3.U.154.238; 3.U.154.239; 3.U.154.154; 3.U.154.157; 3.U.154.166; 3.U.154.169; 3.U.154.172; 3.U.154.175; 3.U.154.240; 3.U.154.244; 3.U.157.228; 3.U.157.229; 3.U.157.230; 3.U.157.231; 3.U.157.236; 3.U.157.237; 3.U.157.238; 3.U.157.239; 3.U.157.154; 3.U.157.157; 3.U.157.166; 3.U.157.169; 3.U.157.172; 3.U.157.175; 3.U.157.240; 3.U.157.244; 3.U.166.228; 3.U.166.229; 3.U.166.230; 3.U.166.231; 3.U.166.236; 3.U.166.237; 3.U.166.238; 3.U.166.239; 3.U.166.154; 3.U.166.157; 3.U.166.166; 3.U.166.169; 3.U.166.172; 3.U.166.175; 3.U.166.240; 3.U.166.244; 3.U.169.228; 3.U.169.229; 3.U.169.230; 3.U.169.231; 3.U.169.236; 3.U.169.237; 3.U.169.238; 3.U.169.239; 3.U.169.154; 3.U.169.157; 3.U.169.166; 3.U.169.169; 3.U.169.172; 3.U.169.175; 3.U.169.240; 3.U.169.244; 3.U.172.228; 3.U.172.229; 3.U.172.230; 3.U.172.231; 3.U.172.236; 3.U.172.237; 3.U.172.238; 3.U.172.239; 3.U.172.154; 3.U.172.157; 3.U.172.166; 3.U.172.169; 3.U.172.172; 3.U.172.175; 3.U.172.240; 3.U.172.244; 3.U.175.228; 3.U.175.229; 3.U.175.230; 3.U.175.231; 3.U.175.236; 3.U.175.237; 3.U.175.238; 3.U.175.239; 3.U.175.154; 3.U.175.157; 3.U.175.166; 3.U.175.169; 3.U.175.172; 3.U.175.175; 3.U.175.240; 3.U.175.244; 3.U.240.228; 3.U.240.229; 3.U.240.230; 3.U.240.231; 3.U.240.236; 3.U.240.237; 3.U.240.238; 3.U.240.239; 3.U.240.154; 3.U.240.157; 3.U.240.166; 3.U.240.169; 3.U.240.172; 3.U.240.175; 3.U.240.240; 3.U.240.244; 3.U.244.228; 3.U.244.229; 3.U.244.230; 3.U.244.231; 3.U.244.236; 3.U.244.237;

3.U.244.238; 3.U.244.239; 3.U.244.154; 3.U.244.157; 3.U.244.166; 3.U.244.169; 3.U.244.172; 3.U.244.175; 3.U.244.240; 3.U.244.244;

Prodrugs of 3.W

3.W.228.228; 3.W.228.229; 3.W.228.230; 3.W.228.231; 3.W.228.236; 3.W.228.237; 3.W.228.238; 3.W.228.239; 3.W.228.154; 3.W.228.157; 3.W.228.166; 3.W.228.169; 3.W.228.172; 3.W.228.175; 3.W.228.240; 3.W.228.244; 3.W.229.228; 3.W.229.229; 3.W.229.230; 3.W.229.231; 3.W.229.236; 3.W.229.237; 3.W.229.238; 3.W.229.239; 3.W.229.154; 3.W.229.157; 3.W.229.166; 3.W.229.169; 3.W.229.172; 3.W.229.175; 3.W.229.240; 3.W.229.244; 3.W.230.228; 3.W.230.229; 3.W.230.230; 3.W.230.231; 3.W.230.236; 3.W.230.237; 3.W.230.238; 3.W.230.239; 3.W.230.154; 3.W.230.157; 3.W.230.166; 3.W.230.169; 3.W.230.172; 3.W.230.175; 3.W.230.240; 3.W.230.244; 3.W.231.228; 3.W.231.229; 3.W.231.230; 3.W.231.231; 3.W.231.236; 3.W.231.237; 3.W.231.238; 3.W.231.239; 3.W.231.154; 3.W.231.157; 3.W.231.166; 3.W.231.169; 3.W.231.172; 3.W.231.175; 3.W.231.240; 3.W.231.244; 3.W.236.228; 3.W.236.229; 3.W.236.230; 3.W.236.231; 3.W.236.236; 3.W.236.237; 3.W.236.238; 3.W.236.239; 3.W.236.154; 3.W.236.157; 3.W.236.166; 3.W.236.169; 3.W.236.172; 3.W.236.175; 3.W.236.240; 3.W.236.244; 3.W.237.228; 3.W.237.229; 3.W.237.230; 3.W.237.231; 3.W.237.236; 3.W.237.237; 3.W.237.238; 3.W.237.239; 3.W.237.154; 3.W.237.157; 3.W.237.166; 3.W.237.169; 3.W.237.172; 3.W.237.175; 3.W.237.240; 3.W.237.244; 3.W.238.228; 3.W.238.229; 3.W.238.230; 3.W.238.231; 3.W.238.236; 3.W.238.237; 3.W.238.238; 3.W.238.239; 3.W.238.154; 3.W.238.157; 3.W.238.166; 3.W.238.169; 3.W.238.172; 3.W.238.175; 3.W.238.240; 3.W.238.244; 3.W.239.228; 3.W.239.229; 3.W.239.230; 3.W.239.231; 3.W.239.236; 3.W.239.237; 3.W.239.238; 3.W.239.239; 3.W.239.154; 3.W.239.157; 3.W.239.166; 3.W.239.169; 3.W.239.172; 3.W.239.175; 3.W.239.240; 3.W.239.244; 3.W.154.228; 3.W.154.229; 3.W.154.230; 3.W.154.231; 3.W.154.236; 3.W.154.237; 3.W.154.238; 3.W.154.239; 3.W.154.154; 3.W.154.157; 3.W.154.166; 3.W.154.169; 3.W.154.172; 3.W.154.175; 3.W.154.240; 3.W.154.244; 3.W.157.228; 3.W.157.229; 3.W.157.230; 3.W.157.231; 3.W.157.236; 3.W.157.237; 3.W.157.238; 3.W.157.239; 3.W.157.154; 3.W.157.157; 3.W.157.166; 3.W.157.169; 3.W.157.172; 3.W.157.175; 3.W.157.240; 3.W.157.244; 3.W.166.228; 3.W.166.229; 3.W.166.230; 3.W.166.231; 3.W.166.236; 3.W.166.237; 3.W.166.238; 3.W.166.239; 3.W.166.154; 3.W.166.157; 3.W.166.166; 3.W.166.169; 3.W.166.172; 3.W.166.175; 3.W.166.240; 3.W.166.244; 3.W.169.228; 3.W.169.229; 3.W.169.230; 3.W.169.231; 3.W.169.236; 3.W.169.237; 3.W.169.238; 3.W.169.239; 3.W.169.154; 3.W.169.157; 3.W.169.166; 3.W.169.169; 3.W.169.172; 3.W.169.175; 3.W.169.240; 3.W.169.244; 3.W.172.228; 3.W.172.229; 3.W.172.230; 3.W.172.231; 3.W.172.236; 3.W.172.237; 3.W.172.238; 3.W.172.239; 3.W.172.154; 3.W.172.157; 3.W.172.166; 3.W.172.169; 3.W.172.172; 3.W.172.175; 3.W.172.240; 3.W.172.244; 3.W.175.228; 3.W.175.229; 3.W.175.230; 3.W.175.231; 3.W.175.236; 3.W.175.237; 3.W.175.238; 3.W.175.239; 3.W.175.154; 3.W.175.157; 3.W.175.166; 3.W.175.169; 3.W.175.172; 3.W.175.175; 3.W.175.240; 3.W.175.244; 3.W.240.228; 3.W.240.229; 3.W.240.230; 3.W.240.231; 3.W.240.236; 3.W.240.237; 3.W.240.238; 3.W.240.239; 3.W.240.154; 3.W.240.157; 3.W.240.166; 3.W.240.169; 3.W.240.172; 3.W.240.175; 3.W.240.240; 3.W.240.244; 3.W.244.228; 3.W.244.229; 3.W.244.230; 3.W.244.231; 3.W.244.236; 3.W.244.237;

3.W.244.238; 3.W.244.239; 3.W.244.154; 3.W.244.157; 3.W.244.166; 3.W.244.169; 3.W.244.172; 3.W.244.175; 3.W.244.240; 3.W.244.244;

Prodrugs of 3.Y

3.Y.228.228; 3.Y.228.229; 3.Y.228.230; 3.Y.228.231; 3.Y.228.236; 3.Y.228.237; 3.Y.228.238; 3.Y.228.239; 3.Y.228.154; 3.Y.228.157; 3.Y.228.166; 3.Y.228.169; 3.Y.228.172; 3.Y.228.175; 3.Y.228.240; 3.Y.228.244; 3.Y.229.228; 3.Y.229.229; 3.Y.229.230; 3.Y.229.231; 3.Y.229.236; 3.Y.229.237; 3.Y.229.238; 3.Y.229.239; 3.Y.229.154; 3.Y.229.157; 3.Y.229.166; 3.Y.229.169; 3.Y.229.172; 3.Y.229.175; 3.Y.229.240; 3.Y.229.244; 3.Y.230.228; 3.Y.230.229; 3.Y.230.230; 3.Y.230.231; 3.Y.230.236; 3.Y.230.237; 3.Y.230.238; 3.Y.230.239; 3.Y.230.154; 3.Y.230.157; 3.Y.230.166; 3.Y.230.169; 3.Y.230.172; 3.Y.230.175; 3.Y.230.240; 3.Y.230.244; 3.Y.231.228; 3.Y.231.229; 3.Y.231.230; 3.Y.231.231; 3.Y.231.236; 3.Y.231.237; 3.Y.231.238; 3.Y.231.239; 3.Y.231.154; 3.Y.231.157; 3.Y.231.166; 3.Y.231.169; 3.Y.231.172; 3.Y.231.175; 3.Y.231.240; 3.Y.231.244; 3.Y.236.228; 3.Y.236.229; 3.Y.236.230; 3.Y.236.231; 3.Y.236.236; 3.Y.236.237; 3.Y.236.238; 3.Y.236.239; 3.Y.236.154; 3.Y.236.157; 3.Y.236.166; 3.Y.236.169; 3.Y.236.172; 3.Y.236.175; 3.Y.236.240; 3.Y.236.244; 3.Y.237.228; 3.Y.237.229; 3.Y.237.230; 3.Y.237.231; 3.Y.237.236; 3.Y.237.237; 3.Y.237.238; 3.Y.237.239; 3.Y.237.154; 3.Y.237.157; 3.Y.237.166; 3.Y.237.169; 3.Y.237.172; 3.Y.237.175; 3.Y.237.240; 3.Y.237.244; 3.Y.238.228; 3.Y.238.229; 3.Y.238.230; 3.Y.238.231; 3.Y.238.236; 3.Y.238.237; 3.Y.238.238; 3.Y.238.239; 3.Y.238.154; 3.Y.238.157; 3.Y.238.166; 3.Y.238.169; 3.Y.238.172; 3.Y.238.175; 3.Y.238.240; 3.Y.238.244; 3.Y.239.228; 3.Y.239.229; 3.Y.239.230; 3.Y.239.231; 3.Y.239.236; 3.Y.239.237; 3.Y.239.238; 3.Y.239.239; 3.Y.239.154; 3.Y.239.157; 3.Y.239.166; 3.Y.239.169; 3.Y.239.172; 3.Y.239.175; 3.Y.239.240; 3.Y.239.244; 3.Y.154.228; 3.Y.154.229; 3.Y.154.230; 3.Y.154.231; 3.Y.154.236; 3.Y.154.237; 3.Y.154.238; 3.Y.154.239; 3.Y.154.154; 3.Y.154.157; 3.Y.154.166; 3.Y.154.169; 3.Y.154.172; 3.Y.154.175; 3.Y.154.240; 3.Y.154.244; 3.Y.157.228; 3.Y.157.229; 3.Y.157.230; 3.Y.157.231; 3.Y.157.236; 3.Y.157.237; 3.Y.157.238; 3.Y.157.239; 3.Y.157.154; 3.Y.157.157; 3.Y.157.166; 3.Y.157.169; 3.Y.157.172; 3.Y.157.175; 3.Y.157.240; 3.Y.157.244; 3.Y.166.228; 3.Y.166.229; 3.Y.166.230; 3.Y.166.231; 3.Y.166.236; 3.Y.166.237; 3.Y.166.238; 3.Y.166.239; 3.Y.166.154; 3.Y.166.157; 3.Y.166.166; 3.Y.166.169; 3.Y.166.172; 3.Y.166.175; 3.Y.166.240; 3.Y.166.244; 3.Y.169.228; 3.Y.169.229; 3.Y.169.230; 3.Y.169.231; 3.Y.169.236; 3.Y.169.237; 3.Y.169.238; 3.Y.169.239; 3.Y.169.154; 3.Y.169.157; 3.Y.169.166; 3.Y.169.169; 3.Y.169.172; 3.Y.169.175; 3.Y.169.240; 3.Y.169.244; 3.Y.172.228; 3.Y.172.229; 3.Y.172.230; 3.Y.172.231; 3.Y.172.236; 3.Y.172.237; 3.Y.172.238; 3.Y.172.239; 3.Y.172.154; 3.Y.172.157; 3.Y.172.166; 3.Y.172.169; 3.Y.172.172; 3.Y.172.175; 3.Y.172.240; 3.Y.172.244; 3.Y.175.228; 3.Y.175.229; 3.Y.175.230; 3.Y.175.231; 3.Y.175.236; 3.Y.175.237; 3.Y.175.238; 3.Y.175.239; 3.Y.175.154; 3.Y.175.157; 3.Y.175.166; 3.Y.175.169; 3.Y.175.172; 3.Y.175.175; 3.Y.175.240; 3.Y.175.244; 3.Y.240.228; 3.Y.240.229; 3.Y.240.230; 3.Y.240.231; 3.Y.240.236; 3.Y.240.237; 3.Y.240.238; 3.Y.240.239; 3.Y.240.154; 3.Y.240.157; 3.Y.240.166; 3.Y.240.169; 3.Y.240.172; 3.Y.240.175; 3.Y.240.240; 3.Y.240.244; 3.Y.244.228; 3.Y.244.229; 3.Y.244.230; 3.Y.244.231; 3.Y.244.236; 3.Y.244.237;

3.Y.244.238; 3.Y.244.239; 3.Y.244.154; 3.Y.244.157; 3.Y.244.166; 3.Y.244.169; 3.Y.244.172; 3.Y.244.175; 3.Y.244.240; 3.Y.244.244;

Prodrugs of 4.B

4.B.228.228; 4.B.228.229; 4.B.228.230; 4.B.228.231; 4.B.228.236; 4.B.228.237; 4.B.228.238; 4.B.228.239; 4.B.228.154; 4.B.228.157; 4.B.228.166; 4.B.228.169; 4.B.228.172; 4.B.228.175; 4.B.228.240; 4.B.228.244; 4.B.229.228; 4.B.229.229; 4.B.229.230; 4.B.229.231; 4.B.229.236; 4.B.229.237; 4.B.229.238; 4.B.229.239; 4.B.229.154; 4.B.229.157; 4.B.229.166; 4.B.229.169; 4.B.229.172; 4.B.229.175; 4.B.229.240; 4.B.229.244; 4.B.230.228; 4.B.230.229; 4.B.230.230; 4.B.230.231; 4.B.230.236; 4.B.230.237; 4.B.230.238; 4.B.230.239; 4.B.230.154; 4.B.230.157; 4.B.230.166; 4.B.230.169; 4.B.230.172; 4.B.230.175; 4.B.230.240; 4.B.230.244; 4.B.231.228; 4.B.231.229; 4.B.231.230; 4.B.231.231; 4.B.231.236; 4.B.231.237; 4.B.231.238; 4.B.231.239; 4.B.231.154; 4.B.231.157; 4.B.231.166; 4.B.231.169; 4.B.231.172; 4.B.231.175; 4.B.231.240; 4.B.231.244; 4.B.236.228; 4.B.236.229; 4.B.236.230; 4.B.236.231; 4.B.236.236; 4.B.236.237; 4.B.236.238; 4.B.236.239; 4.B.236.154; 4.B.236.157; 4.B.236.166; 4.B.236.169; 4.B.236.172; 4.B.236.175; 4.B.236.240; 4.B.236.244; 4.B.237.228; 4.B.237.229; 4.B.237.230; 4.B.237.231; 4.B.237.236; 4.B.237.237; 4.B.237.238; 4.B.237.239; 4.B.237.154; 4.B.237.157; 4.B.237.166; 4.B.237.169; 4.B.237.172; 4.B.237.175; 4.B.237.240; 4.B.237.244; 4.B.238.228; 4.B.238.229; 4.B.238.230; 4.B.238.231; 4.B.238.236; 4.B.238.237; 4.B.238.238; 4.B.238.239; 4.B.238.154; 4.B.238.157; 4.B.238.166; 4.B.238.169; 4.B.238.172; 4.B.238.175; 4.B.238.240; 4.B.238.244; 4.B.239.228; 4.B.239.229; 4.B.239.230; 4.B.239.231; 4.B.239.236; 4.B.239.237; 4.B.239.238; 4.B.239.239; 4.B.239.154; 4.B.239.157; 4.B.239.166; 4.B.239.169; 4.B.239.172; 4.B.239.175; 4.B.239.240; 4.B.239.244; 4.B.154.228; 4.B.154.229; 4.B.154.230; 4.B.154.231; 4.B.154.236; 4.B.154.237; 4.B.154.238; 4.B.154.239; 4.B.154.154; 4.B.154.157; 4.B.154.166; 4.B.154.169; 4.B.154.172; 4.B.154.175; 4.B.154.240; 4.B.154.244; 4.B.157.228; 4.B.157.229; 4.B.157.230; 4.B.157.231; 4.B.157.236; 4.B.157.237; 4.B.157.238; 4.B.157.239; 4.B.157.154; 4.B.157.157; 4.B.157.166; 4.B.157.169; 4.B.157.172; 4.B.157.175; 4.B.157.240; 4.B.157.244; 4.B.166.228; 4.B.166.229; 4.B.166.230; 4.B.166.231; 4.B.166.236; 4.B.166.237; 4.B.166.238; 4.B.166.239; 4.B.166.154; 4.B.166.157; 4.B.166.166; 4.B.166.169; 4.B.166.172; 4.B.166.175; 4.B.166.240; 4.B.166.244; 4.B.169.228; 4.B.169.229; 4.B.169.230; 4.B.169.231; 4.B.169.236; 4.B.169.237; 4.B.169.238; 4.B.169.239; 4.B.169.154; 4.B.169.157; 4.B.169.166; 4.B.169.169; 4.B.169.172; 4.B.169.175; 4.B.169.240; 4.B.169.244; 4.B.172.228; 4.B.172.229; 4.B.172.230; 4.B.172.231; 4.B.172.236; 4.B.172.237; 4.B.172.238; 4.B.172.239; 4.B.172.154; 4.B.172.157; 4.B.172.166; 4.B.172.169; 4.B.172.172; 4.B.172.175; 4.B.172.240; 4.B.172.244; 4.B.175.228; 4.B.175.229; 4.B.175.230; 4.B.175.231; 4.B.175.236; 4.B.175.237; 4.B.175.238; 4.B.175.239; 4.B.175.154; 4.B.175.157; 4.B.175.166; 4.B.175.169; 4.B.175.172; 4.B.175.175; 4.B.175.240; 4.B.175.244; 4.B.240.228; 4.B.240.229; 4.B.240.230; 4.B.240.231; 4.B.240.236; 4.B.240.237; 4.B.240.238; 4.B.240.239; 4.B.240.154; 4.B.240.157; 4.B.240.166; 4.B.240.169; 4.B.240.172; 4.B.240.175; 4.B.240.240; 4.B.240.244; 4.B.244.228; 4.B.244.229; 4.B.244.230; 4.B.244.231; 4.B.244.236; 4.B.244.237; 4.B.244.238; 4.B.244.239; 4.B.244.154; 4.B.244.157; 4.B.244.166; 4.B.244.169; 4.B.244.172; 4.B.244.175; 4.B.244.240; 4.B.244.244;

Prodrugs of 4.D

4.D.228.228; 4.D.228.229; 4.D.228.230; 4.D.228.231; 4.D.228.236; 4.D.228.237; 4.D.228.238; 4.D.228.239; 4.D.228.154; 4.D.228.157; 4.D.228.166; 4.D.228.169; 4.D.228.172; 4.D.228.175; 4.D.228.240; 4.D.228.244; 4.D.229.228; 4.D.229.229;

4.D.229.230; 4.D.229.231; 4.D.229.236; 4.D.229.237; 4.D.229.238; 4.D.229.239; 4.D.229.154; 4.D.229.157; 4.D.229.166; 4.D.229.169; 4.D.229.172; 4.D.229.175; 4.D.229.240; 4.D.229.244; 4.D.230.228; 4.D.230.229; 4.D.230.230; 4.D.230.231; 4.D.230.236; 4.D.230.237; 4.D.230.238; 4.D.230.239; 4.D.230.154; 4.D.230.157; 4.D.230.166; 4.D.230.169; 4.D.230.172; 4.D.230.175; 4.D.230.240; 4.D.230.244; 4.D.231.228; 4.D.231.229; 4.D.231.230; 4.D.231.231; 4.D.231.236; 4.D.231.237; 4.D.231.238; 4.D.231.239; 4.D.231.154; 4.D.231.157; 4.D.231.166; 4.D.231.169; 4.D.231.172; 4.D.231.175; 4.D.231.240; 4.D.231.244; 4.D.236.228; 4.D.236.229; 4.D.236.230; 4.D.236.231; 4.D.236.236; 4.D.236.237; 4.D.236.238; 4.D.236.239; 4.D.236.154; 4.D.236.157; 4.D.236.166; 4.D.236.169; 4.D.236.172; 4.D.236.175; 4.D.236.240; 4.D.236.244; 4.D.237.228; 4.D.237.229; 4.D.237.230; 4.D.237.231; 4.D.237.236; 4.D.237.237; 4.D.237.238; 4.D.237.239; 4.D.237.154; 4.D.237.157; 4.D.237.166; 4.D.237.169; 4.D.237.172; 4.D.237.175; 4.D.237.240; 4.D.237.244; 4.D.238.228; 4.D.238.229; 4.D.238.230; 4.D.238.231; 4.D.238.236; 4.D.238.237; 4.D.238.238; 4.D.238.239; 4.D.238.154; 4.D.238.157; 4.D.238.166; 4.D.238.169; 4.D.238.172; 4.D.238.175; 4.D.238.240; 4.D.238.244; 4.D.239.228; 4.D.239.229; 4.D.239.230; 4.D.239.231; 4.D.239.236; 4.D.239.237; 4.D.239.238; 4.D.239.239; 4.D.239.154; 4.D.239.157; 4.D.239.166; 4.D.239.169; 4.D.239.172; 4.D.239.175; 4.D.239.240; 4.D.239.244; 4.D.154.228; 4.D.154.229; 4.D.154.230; 4.D.154.231; 4.D.154.236; 4.D.154.237; 4.D.154.238; 4.D.154.239; 4.D.154.154; 4.D.154.157; 4.D.154.166; 4.D.154.169; 4.D.154.172; 4.D.154.175; 4.D.154.240; 4.D.154.244; 4.D.157.228; 4.D.157.229; 4.D.157.230; 4.D.157.231; 4.D.157.236; 4.D.157.237; 4.D.157.238; 4.D.157.239; 4.D.157.154; 4.D.157.157; 4.D.157.166; 4.D.157.169; 4.D.157.172; 4.D.157.175; 4.D.157.240; 4.D.157.244; 4.D.166.228; 4.D.166.229; 4.D.166.230; 4.D.166.231; 4.D.166.236; 4.D.166.237; 4.D.166.238; 4.D.166.239; 4.D.166.154; 4.D.166.157; 4.D.166.166; 4.D.166.169; 4.D.166.172; 4.D.166.175; 4.D.166.240; 4.D.166.244; 4.D.169.228; 4.D.169.229; 4.D.169.230; 4.D.169.231; 4.D.169.236; 4.D.169.237; 4.D.169.238; 4.D.169.239; 4.D.169.154; 4.D.169.157; 4.D.169.166; 4.D.169.169; 4.D.169.172; 4.D.169.175; 4.D.169.240; 4.D.169.244; 4.D.172.228; 4.D.172.229; 4.D.172.230; 4.D.172.231; 4.D.172.236; 4.D.172.237; 4.D.172.238; 4.D.172.239; 4.D.172.154; 4.D.172.157; 4.D.172.166; 4.D.172.169; 4.D.172.172; 4.D.172.175; 4.D.172.240; 4.D.172.244; 4.D.175.228; 4.D.175.229; 4.D.175.230; 4.D.175.231; 4.D.175.236; 4.D.175.237; 4.D.175.238; 4.D.175.239; 4.D.175.154; 4.D.175.157; 4.D.175.166; 4.D.175.169; 4.D.175.172; 4.D.175.175; 4.D.175.240; 4.D.175.244; 4.D.240.228; 4.D.240.229; 4.D.240.230; 4.D.240.231; 4.D.240.236; 4.D.240.237; 4.D.240.238; 4.D.240.239; 4.D.240.154; 4.D.240.157; 4.D.240.166; 4.D.240.169; 4.D.240.172; 4.D.240.175; 4.D.240.240; 4.D.240.244; 4.D.244.228; 4.D.244.229; 4.D.244.230; 4.D.244.231; 4.D.244.236; 4.D.244.237; 4.D.244.238; 4.D.244.239; 4.D.244.154; 4.D.244.157; 4.D.244.166; 4.D.244.169; 4.D.244.172; 4.D.244.175; 4.D.244.240; 4.D.244.244;

<u>Prodrugs of 4.E</u>

4.E.228.228; 4.E.228.229; 4.E.228.230; 4.E.228.231; 4.E.228.236; 4.E.228.237; 4.E.228.238; 4.E.228.239; 4.E.228.154; 4.E.228.157; 4.E.228.166; 4.E.228.169; 4.E.228.172; 4.E.228.175; 4.E.228.240; 4.E.228.244; 4.E.229.228; 4.E.229.229; 4.E.229.230; 4.E.229.231; 4.E.229.236; 4.E.229.237; 4.E.229.238; 4.E.229.239; 4.E.229.154; 4.E.229.157; 4.E.229.166;

4.E.229.169; 4.E.229.172; 4.E.229.175; 4.E.229.240; 4.E.229.244; 4.E.230.228; 4.E.230.229; 4.E.230.230; 4.E.230.231; 4.E.230.236; 4.E.230.237; 4.E.230.238; 4.E.230.239; 4.E.230.154; 4.E.230.157; 4.E.230.166; 4.E.230.169; 4.E.230.172; 4.E.230.175; 4.E.230.240; 4.E.230.244; 4.E.231.228; 4.E.231.229; 4.E.231.230; 4.E.231.231; 4.E.231.236; 4.E.231.237; 4.E.231.238; 4.E.231.239; 4.E.231.154; 4.E.231.157; 4.E.231.166; 4.E.231.169; 4.E.231.172; 4.E.231.175; 4.E.231.240; 4.E.231.244; 4.E.236.228; 4.E.236.229; 4.E.236.230; 4.E.236.231; 4.E.236.236; 4.E.236.237; 4.E.236.238; 4.E.236.239; 4.E.236.154; 4.E.236.157; 4.E.236.166; 4.E.236.169; 4.E.236.172; 4.E.236.175; 4.E.236.240; 4.E.236.244; 4.E.237.228; 4.E.237.229; 4.E.237.230; 4.E.237.231; 4.E.237.236; 4.E.237.237; 4.E.237.238; 4.E.237.239; 4.E.237.154; 4.E.237.157; 4.E.237.166; 4.E.237.169; 4.E.237.172; 4.E.237.175; 4.E.237.240; 4.E.237.244; 4.E.238.228; 4.E.238.229; 4.E.238.230; 4.E.238.231; 4.E.238.236; 4.E.238.237; 4.E.238.238; 4.E.238.239; 4.E.238.154; 4.E.238.157; 4.E.238.166; 4.E.238.169; 4.E.238.172; 4.E.238.175; 4.E.238.240; 4.E.238.244; 4.E.239.228; 4.E.239.229; 4.E.239.230; 4.E.239.231; 4.E.239.236; 4.E.239.237; 4.E.239.238; 4.E.239.239; 4.E.239.154; 4.E.239.157; 4.E.239.166; 4.E.239.169; 4.E.239.172; 4.E.239.175; 4.E.239.240; 4.E.239.244; 4.E.154.228; 4.E.154.229; 4.E.154.230; 4.E.154.231; 4.E.154.236; 4.E.154.237; 4.E.154.238; 4.E.154.239; 4.E.154.154; 4.E.154.157; 4.E.154.166; 4.E.154.169; 4.E.154.172; 4.E.154.175; 4.E.154.240; 4.E.154.244; 4.E.157.228; 4.E.157.229; 4.E.157.230; 4.E.157.231; 4.E.157.236; 4.E.157.237; 4.E.157.238; 4.E.157.239; 4.E.157.154; 4.E.157.157; 4.E.157.166; 4.E.157.169; 4.E.157.172; 4.E.157.175; 4.E.157.240; 4.E.157.244; 4.E.166.228; 4.E.166.229; 4.E.166.230; 4.E.166.231; 4.E.166.236; 4.E.166.237; 4.E.166.238; 4.E.166.239; 4.E.166.154; 4.E.166.157; 4.E.166.166; 4.E.166.169; 4.E.166.172; 4.E.166.175; 4.E.166.240; 4.E.166.244; 4.E.169.228; 4.E.169.229; 4.E.169.230; 4.E.169.231; 4.E.169.236; 4.E.169.237; 4.E.169.238; 4.E.169.239; 4.E.169.154; 4.E.169.157; 4.E.169.166; 4.E.169.169; 4.E.169.172; 4.E.169.175; 4.E.169.240; 4.E.169.244; 4.E.172.228; 4.E.172.229; 4.E.172.230; 4.E.172.231; 4.E.172.236; 4.E.172.237; 4.E.172.238; 4.E.172.239; 4.E.172.154; 4.E.172.157; 4.E.172.166; 4.E.172.169; 4.E.172.172; 4.E.172.175; 4.E.172.240; 4.E.172.244; 4.E.175.228; 4.E.175.229; 4.E.175.230; 4.E.175.231; 4.E.175.236; 4.E.175.237; 4.E.175.238; 4.E.175.239; 4.E.175.154; 4.E.175.157; 4.E.175.166; 4.E.175.169; 4.E.175.172; 4.E.175.175; 4.E.175.240; 4.E.175.244; 4.E.240.228; 4.E.240.229; 4.E.240.230; 4.E.240.231; 4.E.240.236; 4.E.240.237; 4.E.240.238; 4.E.240.239; 4.E.240.154; 4.E.240.157; 4.E.240.166; 4.E.240.169; 4.E.240.172; 4.E.240.175; 4.E.240.240; 4.E.240.244; 4.E.244.228; 4.E.244.229; 4.E.244.230; 4.E.244.231; 4.E.244.236; 4.E.244.237; 4.E.244.238; 4.E.244.239; 4.E.244.154; 4.E.244.157; 4.E.244.166; 4.E.244.169; 4.E.244.172; 4.E.244.175; 4.E.244.240; 4.E.244.244;

<u>Prodrugs of 4.G</u>

4.G.228.228; 4.G.228.229; 4.G.228.230; 4.G.228.231; 4.G.228.236; 4.G.228.237; 4.G.228.238; 4.G.228.239; 4.G.228.154; 4.G.228.157; 4.G.228.166; 4.G.228.169; 4.G.228.172; 4.G.228.175; 4.G.228.240; 4.G.228.244; 4.G.229.228; 4.G.229.229; 4.G.229.230; 4.G.229.231; 4.G.229.236; 4.G.229.237; 4.G.229.238; 4.G.229.239; 4.G.229.154; 4.G.229.157; 4.G.229.166; 4.G.229.169; 4.G.229.172; 4.G.229.175; 4.G.229.240; 4.G.229.244; 4.G.230.228; 4.G.230.229; 4.G.230.230; 4.G.230.231; 4.G.230.236; 4.G.230.237; 4.G.230.238; 4.G.230.239; 4.G.230.154; 4.G.230.157; 4.G.230.166; 4.G.230.169; 4.G.230.172; 4.G.230.175; 4.G.230.240; 4.G.230.244; 4.G.231.228; 4.G.231.229; 4.G.231.230; 4.G.231.231; 4.G.231.236; 4.G.231.237; 4.G.231.238; 4.G.231.239; 4.G.231.154; 4.G.231.157; 4.G.231.166; 4.G.231.169; 4.G.231.172; 4.G.231.175; 4.G.231.240; 4.G.231.244; 4.G.236.228; 4.G.236.229;

4.G.236.230; 4.G.236.231; 4.G.236.236; 4.G.236.237; 4.G.236.238; 4.G.236.239; 4.G.236.154; 4.G.236.157; 4.G.236.166; 4.G.236.169; 4.G.236.172; 4.G.236.175; 4.G.236.240; 4.G.236.244; 4.G.237.228; 4.G.237.229; 4.G.237.230; 4.G.237.231; 4.G.237.236; 4.G.237.237; 4.G.237.238; 4.G.237.239; 4.G.237.154; 4.G.237.157; 4.G.237.166; 4.G.237.169; 4.G.237.172; 4.G.237.175; 4.G.237.240; 4.G.237.244; 4.G.238.228; 4.G.238.229; 4.G.238.230; 4.G.238.231; 4.G.238.236; 4.G.238.237; 4.G.238.238; 4.G.238.239; 4.G.238.154; 4.G.238.157; 4.G.238.166; 4.G.238.169; 4.G.238.172; 4.G.238.175; 4.G.238.240; 4.G.238.244; 4.G.239.228; 4.G.239.229; 4.G.239.230; 4.G.239.231; 4.G.239.236; 4.G.239.237; 4.G.239.238; 4.G.239.239; 4.G.239.154; 4.G.239.157; 4.G.239.166; 4.G.239.169; 4.G.239.172; 4.G.239.175; 4.G.239.240; 4.G.239.244; 4.G.154.228; 4.G.154.229; 4.G.154.230; 4.G.154.231; 4.G.154.236; 4.G.154.237; 4.G.154.238; 4.G.154.239; 4.G.154.154; 4.G.154.157; 4.G.154.166; 4.G.154.169; 4.G.154.172; 4.G.154.175; 4.G.154.240; 4.G.154.244; 4.G.157.228; 4.G.157.229; 4.G.157.230; 4.G.157.231; 4.G.157.236; 4.G.157.237; 4.G.157.238; 4.G.157.239; 4.G.157.154; 4.G.157.157; 4.G.157.166; 4.G.157.169; 4.G.157.172; 4.G.157.175; 4.G.157.240; 4.G.157.244; 4.G.166.228; 4.G.166.229; 4.G.166.230; 4.G.166.231; 4.G.166.236; 4.G.166.237; 4.G.166.238; 4.G.166.239; 4.G.166.154; 4.G.166.157; 4.G.166.166; 4.G.166.169; 4.G.166.172; 4.G.166.175; 4.G.166.240; 4.G.166.244; 4.G.169.228; 4.G.169.229; 4.G.169.230; 4.G.169.231; 4.G.169.236; 4.G.169.237; 4.G.169.238; 4.G.169.239; 4.G.169.154; 4.G.169.157; 4.G.169.166; 4.G.169.169; 4.G.169.172; 4.G.169.175; 4.G.169.240; 4.G.169.244; 4.G.172.228; 4.G.172.229; 4.G.172.230; 4.G.172.231; 4.G.172.236; 4.G.172.237; 4.G.172.238; 4.G.172.239; 4.G.172.154; 4.G.172.157; 4.G.172.166; 4.G.172.169; 4.G.172.172; 4.G.172.175; 4.G.172.240; 4.G.172.244; 4.G.175.228; 4.G.175.229; 4.G.175.230; 4.G.175.231; 4.G.175.236; 4.G.175.237; 4.G.175.238; 4.G.175.239; 4.G.175.154; 4.G.175.157; 4.G.175.166; 4.G.175.169; 4.G.175.172; 4.G.175.175; 4.G.175.240; 4.G.175.244; 4.G.240.228; 4.G.240.229; 4.G.240.230; 4.G.240.231; 4.G.240.236; 4.G.240.237; 4.G.240.238; 4.G.240.239; 4.G.240.154; 4.G.240.157; 4.G.240.166; 4.G.240.169; 4.G.240.172; 4.G.240.175; 4.G.240.240; 4.G.240.244; 4.G.244.228; 4.G.244.229; 4.G.244.230; 4.G.244.231; 4.G.244.236; 4.G.244.237; 4.G.244.238; 4.G.244.239; 4.G.244.154; 4.G.244.157; 4.G.244.166; 4.G.244.169; 4.G.244.172; 4.G.244.175; 4.G.244.240; 4.G.244.244;

Prodrugs of 4.I

4.I.228.228; 4.I.228.229; 4.I.228.230; 4.I.228.231; 4.I.228.236; 4.I.228.237; 4.I.228.238; 4.I.228.239; 4.I.228.154; 4.I.228.157; 4.I.228.166; 4.I.228.169; 4.I.228.172; 4.I.228.175; 4.I.228.240; 4.I.228.244; 4.I.229.228; 4.I.229.229; 4.I.229.230; 4.I.229.231; 4.I.229.236; 4.I.229.237; 4.I.229.238; 4.I.229.239; 4.I.229.154; 4.I.229.157; 4.I.229.166; 4.I.229.169; 4.I.229.172; 4.I.229.175; 4.I.229.240; 4.I.229.244; 4.I.230.228; 4.I.230.229; 4.I.230.230; 4.I.230.231; 4.I.230.236; 4.I.230.237; 4.I.230.238; 4.I.230.239; 4.I.230.154; 4.I.230.157; 4.I.230.166; 4.I.230.169; 4.I.230.172; 4.I.230.175; 4.I.230.240; 4.I.230.244; 4.I.231.228; 4.I.231.229; 4.I.231.230; 4.I.231.231; 4.I.231.236; 4.I.231.237; 4.I.231.238; 4.I.231.239; 4.I.231.154; 4.I.231.157; 4.I.231.166; 4.I.231.169; 4.I.231.172; 4.I.231.175; 4.I.231.240; 4.I.231.244; 4.I.236.228; 4.I.236.229; 4.I.236.230; 4.I.236.231; 4.I.236.236; 4.I.236.237; 4.I.236.238; 4.I.236.239; 4.I.236.154; 4.I.236.157; 4.I.236.166; 4.I.236.169; 4.I.236.172; 4.I.236.175; 4.I.236.240; 4.I.236.244; 4.I.237.228; 4.I.237.229; 4.I.237.230; 4.I.237.231;

4.I.237.236; 4.I.237.237; 4.I.237.238; 4.I.237.239; 4.I.237.154; 4.I.237.157; 4.I.237.166; 4.I.237.169; 4.I.237.172; 4.I.237.175; 4.I.237.240; 4.I.237.244; 4.I.238.228; 4.I.238.229; 4.I.238.230; 4.I.238.231; 4.I.238.236; 4.I.238.237; 4.I.238.238; 4.I.238.239; 4.I.238.154; 4.I.238.157; 4.I.238.166; 4.I.238.169; 4.I.238.172; 4.I.238.175; 4.I.238.240; 4.I.238.244; 4.I.239.228; 4.I.239.229; 4.I.239.230; 4.I.239.231; 4.I.239.236; 4.I.239.237; 4.I.239.238; 4.I.239.239; 4.I.239.154; 4.I.239.157; 4.I.239.166; 4.I.239.169; 4.I.239.172; 4.I.239.175; 4.I.239.240; 4.I.239.244; 4.I.154.228; 4.I.154.229; 4.I.154.230; 4.I.154.231; 4.I.154.236; 4.I.154.237; 4.I.154.238; 4.I.154.239; 4.I.154.154; 4.I.154.157; 4.I.154.166; 4.I.154.169; 4.I.154.172; 4.I.154.175; 4.I.154.240; 4.I.154.244; 4.I.157.228; 4.I.157.229; 4.I.157.230; 4.I.157.231; 4.I.157.236; 4.I.157.237; 4.I.157.238; 4.I.157.239; 4.I.157.154; 4.I.157.157; 4.I.157.166; 4.I.157.169; 4.I.157.172; 4.I.157.175; 4.I.157.240; 4.I.157.244; 4.I.166.228; 4.I.166.229; 4.I.166.230; 4.I.166.231; 4.I.166.236; 4.I.166.237; 4.I.166.238; 4.I.166.239; 4.I.166.154; 4.I.166.157; 4.I.166.166; 4.I.166.169; 4.I.166.172; 4.I.166.175; 4.I.166.240; 4.I.166.244; 4.I.169.228; 4.I.169.229; 4.I.169.230; 4.I.169.231; 4.I.169.236; 4.I.169.237; 4.I.169.238; 4.I.169.239; 4.I.169.154; 4.I.169.157; 4.I.169.166; 4.I.169.169; 4.I.169.172; 4.I.169.175; 4.I.169.240; 4.I.169.244; 4.I.172.228; 4.I.172.229; 4.I.172.230; 4.I.172.231; 4.I.172.236; 4.I.172.237; 4.I.172.238; 4.I.172.239; 4.I.172.154; 4.I.172.157; 4.I.172.166; 4.I.172.169; 4.I.172.172; 4.I.172.175; 4.I.172.240; 4.I.172.244; 4.I.175.228; 4.I.175.229; 4.I.175.230; 4.I.175.231; 4.I.175.236; 4.I.175.237; 4.I.175.238; 4.I.175.239; 4.I.175.154; 4.I.175.157; 4.I.175.166; 4.I.175.169; 4.I.175.172; 4.I.175.175; 4.I.175.240; 4.I.175.244; 4.I.240.228; 4.I.240.229; 4.I.240.230; 4.I.240.231; 4.I.240.236; 4.I.240.237; 4.I.240.238; 4.I.240.239; 4.I.240.154; 4.I.240.157; 4.I.240.166; 4.I.240.169; 4.I.240.172; 4.I.240.175; 4.I.240.240; 4.I.240.244; 4.I.244.228; 4.I.244.229; 4.I.244.230; 4.I.244.231; 4.I.244.236; 4.I.244.237; 4.I.244.238; 4.I.244.239; 4.I.244.154; 4.I.244.157; 4.I.244.166; 4.I.244.169; 4.I.244.172; 4.I.244.175; 4.I.244.240; 4.I.244.244;

<u>Prodrugs of 4.J</u>

4.J.228.228; 4.J.228.229; 4.J.228.230; 4.J.228.231; 4.J.228.236; 4.J.228.237; 4.J.228.238; 4.J.228.239; 4.J.228.154; 4.J.228.157; 4.J.228.166; 4.J.228.169; 4.J.228.172; 4.J.228.175; 4.J.228.240; 4.J.228.244; 4.J.229.228; 4.J.229.229; 4.J.229.230; 4.J.229.231; 4.J.229.236; 4.J.229.237; 4.J.229.238; 4.J.229.239; 4.J.229.154; 4.J.229.157; 4.J.229.166; 4.J.229.169; 4.J.229.172; 4.J.229.175; 4.J.229.240; 4.J.229.244; 4.J.230.228; 4.J.230.229; 4.J.230.230; 4.J.230.231; 4.J.230.236; 4.J.230.237; 4.J.230.238; 4.J.230.239; 4.J.230.154; 4.J.230.157; 4.J.230.166; 4.J.230.169; 4.J.230.172; 4.J.230.175; 4.J.230.240; 4.J.230.244; 4.J.231.228; 4.J.231.229; 4.J.231.230; 4.J.231.231; 4.J.231.236; 4.J.231.237; 4.J.231.238; 4.J.231.239; 4.J.231.154; 4.J.231.157; 4.J.231.166; 4.J.231.169; 4.J.231.172; 4.J.231.175; 4.J.231.240; 4.J.231.244; 4.J.236.228; 4.J.236.229; 4.J.236.230; 4.J.236.231; 4.J.236.236; 4.J.236.237; 4.J.236.238; 4.J.236.239; 4.J.236.154; 4.J.236.157; 4.J.236.166; 4.J.236.169; 4.J.236.172; 4.J.236.175; 4.J.236.240; 4.J.236.244; 4.J.237.228; 4.J.237.229; 4.J.237.230; 4.J.237.231; 4.J.237.236; 4.J.237.237; 4.J.237.238; 4.J.237.239; 4.J.237.154; 4.J.237.157; 4.J.237.166; 4.J.237.169; 4.J.237.172; 4.J.237.175; 4.J.237.240; 4.J.237.244; 4.J.238.228; 4.J.238.229; 4.J.238.230; 4.J.238.231; 4.J.238.236; 4.J.238.237; 4.J.238.238; 4.J.238.239; 4.J.238.154; 4.J.238.157; 4.J.238.166; 4.J.238.169; 4.J.238.172; 4.J.238.175; 4.J.238.240; 4.J.238.244; 4.J.239.228; 4.J.239.229; 4.J.239.230; 4.J.239.231; 4.J.239.236; 4.J.239.237; 4.J.239.238; 4.J.239.239; 4.J.239.154; 4.J.239.157; 4.J.239.166; 4.J.239.169; 4.J.239.172; 4.J.239.175; 4.J.239.240; 4.J.239.244; 4.J.154.228; 4.J.154.229; 4.J.154.230; 4.J.154.231; 4.J.154.236;

4.J.154.237; 4.J.154.238; 4.J.154.239; 4.J.154.154; 4.J.154.157; 4.J.154.166; 4.J.154.169; 4.J.154.172; 4.J.154.175; 4.J.154.240; 4.J.154.244; 4.J.157.228; 4.J.157.229; 4.J.157.230; 4.J.157.231; 4.J.157.236; 4.J.157.237; 4.J.157.238; 4.J.157.239; 4.J.157.154; 4.J.157.157; 4.J.157.166; 4.J.157.169; 4.J.157.172; 4.J.157.175; 4.J.157.240; 4.J.157.244; 4.J.166.228; 4.J.166.229; 4.J.166.230; 4.J.166.231; 4.J.166.236; 4.J.166.237; 4.J.166.238; 4.J.166.239; 4.J.166.154; 4.J.166.157; 4.J.166.166; 4.J.166.169; 4.J.166.172; 4.J.166.175; 4.J.166.240; 4.J.166.244; 4.J.169.228; 4.J.169.229; 4.J.169.230; 4.J.169.231; 4.J.169.236; 4.J.169.237; 4.J.169.238; 4.J.169.239; 4.J.169.154; 4.J.169.157; 4.J.169.166; 4.J.169.169; 4.J.169.172; 4.J.169.175; 4.J.169.240; 4.J.169.244; 4.J.172.228; 4.J.172.229; 4.J.172.230; 4.J.172.231; 4.J.172.236; 4.J.172.237; 4.J.172.238; 4.J.172.239; 4.J.172.154; 4.J.172.157; 4.J.172.166; 4.J.172.169; 4.J.172.172; 4.J.172.175; 4.J.172.240; 4.J.172.244; 4.J.175.228; 4.J.175.229; 4.J.175.230; 4.J.175.231; 4.J.175.236; 4.J.175.237; 4.J.175.238; 4.J.175.239; 4.J.175.154; 4.J.175.157; 4.J.175.166; 4.J.175.169; 4.J.175.172; 4.J.175.175; 4.J.175.240; 4.J.175.244; 4.J.240.228; 4.J.240.229; 4.J.240.230; 4.J.240.231; 4.J.240.236; 4.J.240.237; 4.J.240.238; 4.J.240.239; 4.J.240.154; 4.J.240.157; 4.J.240.166; 4.J.240.169; 4.J.240.172; 4.J.240.175; 4.J.240.240; 4.J.240.244; 4.J.244.228; 4.J.244.229; 4.J.244.230; 4.J.244.231; 4.J.244.236; 4.J.244.237; 4.J.244.238; 4.J.244.239; 4.J.244.154; 4.J.244.157; 4.J.244.166; 4.J.244.169; 4.J.244.172; 4.J.244.175; 4.J.244.240; 4.J.244.244;

Prodrugs of 4.L

4.L.228.228; 4.L.228.229; 4.L.228.230; 4.L.228.231; 4.L.228.236; 4.L.228.237; 4.L.228.238; 4.L.228.239; 4.L.228.154; 4.L.228.157; 4.L.228.166; 4.L.228.169; 4.L.228.172; 4.L.228.175; 4.L.228.240; 4.L.228.244; 4.L.229.228; 4.L.229.229; 4.L.229.230; 4.L.229.231; 4.L.229.236; 4.L.229.237; 4.L.229.238; 4.L.229.239; 4.L.229.154; 4.L.229.157; 4.L.229.166; 4.L.229.169; 4.L.229.172; 4.L.229.175; 4.L.229.240; 4.L.229.244; 4.L.230.228; 4.L.230.229; 4.L.230.230; 4.L.230.231; 4.L.230.236; 4.L.230.237; 4.L.230.238; 4.L.230.239; 4.L.230.154; 4.L.230.157; 4.L.230.166; 4.L.230.169; 4.L.230.172; 4.L.230.175; 4.L.230.240; 4.L.230.244; 4.L.231.228; 4.L.231.229; 4.L.231.230; 4.L.231.231; 4.L.231.236; 4.L.231.237; 4.L.231.238; 4.L.231.239; 4.L.231.154; 4.L.231.157; 4.L.231.166; 4.L.231.169; 4.L.231.172; 4.L.231.175; 4.L.231.240; 4.L.231.244; 4.L.236.228; 4.L.236.229; 4.L.236.230; 4.L.236.231; 4.L.236.236; 4.L.236.237; 4.L.236.238; 4.L.236.239; 4.L.236.154; 4.L.236.157; 4.L.236.166; 4.L.236.169; 4.L.236.172; 4.L.236.175; 4.L.236.240; 4.L.236.244; 4.L.237.228; 4.L.237.229; 4.L.237.230; 4.L.237.231; 4.L.237.236; 4.L.237.237; 4.L.237.238; 4.L.237.239; 4.L.237.154; 4.L.237.157; 4.L.237.166; 4.L.237.169; 4.L.237.172; 4.L.237.175; 4.L.237.240; 4.L.237.244; 4.L.238.228; 4.L.238.229; 4.L.238.230; 4.L.238.231; 4.L.238.236; 4.L.238.237; 4.L.238.238; 4.L.238.239; 4.L.238.154; 4.L.238.157; 4.L.238.166; 4.L.238.169; 4.L.238.172; 4.L.238.175; 4.L.238.240; 4.L.238.244; 4.L.239.228; 4.L.239.229; 4.L.239.230; 4.L.239.231; 4.L.239.236; 4.L.239.237; 4.L.239.238; 4.L.239.239; 4.L.239.154; 4.L.239.157; 4.L.239.166; 4.L.239.169; 4.L.239.172; 4.L.239.175; 4.L.239.240; 4.L.239.244; 4.L.154.228; 4.L.154.229; 4.L.154.230; 4.L.154.231; 4.L.154.236; 4.L.154.237; 4.L.154.238; 4.L.154.239; 4.L.154.154; 4.L.154.157; 4.L.154.166; 4.L.154.169; 4.L.154.172; 4.L.154.175; 4.L.154.240; 4.L.154.244; 4.L.157.228; 4.L.157.229; 4.L.157.230; 4.L.157.231; 4.L.157.236; 4.L.157.237; 4.L.157.238; 4.L.157.239; 4.L.157.154; 4.L.157.157; 4.L.157.166; 4.L.157.169; 4.L.157.172; 4.L.157.175; 4.L.157.240; 4.L.157.244; 4.L.166.228; 4.L.166.229; 4.L.166.230; 4.L.166.231; 4.L.166.236; 4.L.166.237; 4.L.166.238; 4.L.166.239; 4.L.166.154; 4.L.166.157; 4.L.166.166; 4.L.166.169; 4.L.166.172; 4.L.166.175; 4.L.166.240; 4.L.166.244; 4.L.169.228; 4.L.169.229; 4.L.169.230; 4.L.169.231; 4.L.169.236;

4.L.169.237; 4.L.169.238; 4.L.169.239; 4.L.169.154; 4.L.169.157; 4.L.169.166; 4.L.169.169; 4.L.169.172; 4.L.169.175; 4.L.169.240; 4.L.169.244; 4.L.172.228; 4.L.172.229; 4.L.172.230; 4.L.172.231; 4.L.172.236; 4.L.172.237; 4.L.172.238; 4.L.172.239; 4.L.172.154; 4.L.172.157; 4.L.172.166; 4.L.172.169; 4.L.172.172; 4.L.172.175; 4.L.172.240; 4.L.172.244; 4.L.175.228; 4.L.175.229; 4.L.175.230; 4.L.175.231; 4.L.175.236; 4.L.175.237; 4.L.175.238; 4.L.175.239; 4.L.175.154; 4.L.175.157; 4.L.175.166; 4.L.175.169; 4.L.175.172; 4.L.175.175; 4.L.175.240; 4.L.175.244; 4.L.240.228; 4.L.240.229; 4.L.240.230; 4.L.240.231; 4.L.240.236; 4.L.240.237; 4.L.240.238; 4.L.240.239; 4.L.240.154; 4.L.240.157; 4.L.240.166; 4.L.240.169; 4.L.240.172; 4.L.240.175; 4.L.240.240; 4.L.240.244; 4.L.244.228; 4.L.244.229; 4.L.244.230; 4.L.244.231; 4.L.244.236; 4.L.244.237; 4.L.244.238; 4.L.244.239; 4.L.244.154; 4.L.244.157; 4.L.244.166; 4.L.244.169; 4.L.244.172; 4.L.244.175; 4.L.244.240; 4.L.244.244;

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4.O.228.228; 4.O.228.229; 4.O.228.230; 4.O.228.231; 4.O.228.236; 4.O.228.237; 4.O.228.238; 4.O.228.239; 4.O.228.154; 4.O.228.157; 4.O.228.166; 4.O.228.169; 4.O.228.172; 4.O.228.175; 4.O.228.240; 4.O.228.244; 4.O.229.228; 4.O.229.229; 4.O.229.230; 4.O.229.231; 4.O.229.236; 4.O.229.237; 4.O.229.238; 4.O.229.239; 4.O.229.154; 4.O.229.157; 4.O.229.166; 4.O.229.169; 4.O.229.172; 4.O.229.175; 4.O.229.240; 4.O.229.244; 4.O.230.228; 4.O.230.229; 4.O.230.230; 4.O.230.231; 4.O.230.236; 4.O.230.237; 4.O.230.238; 4.O.230.239; 4.O.230.154; 4.O.230.157; 4.O.230.166; 4.O.230.169; 4.O.230.172; 4.O.230.175; 4.O.230.240; 4.O.230.244; 4.O.231.228; 4.O.231.229; 4.O.231.230; 4.O.231.231; 4.O.231.236; 4.O.231.237; 4.O.231.238; 4.O.231.239; 4.O.231.154; 4.O.231.157; 4.O.231.166; 4.O.231.169; 4.O.231.172; 4.O.231.175; 4.O.231.240; 4.O.231.244; 4.O.236.228; 4.O.236.229; 4.O.236.230; 4.O.236.231; 4.O.236.236; 4.O.236.237; 4.O.236.238; 4.O.236.239; 4.O.236.154; 4.O.236.157; 4.O.236.166; 4.O.236.169; 4.O.236.172; 4.O.236.175; 4.O.236.240; 4.O.236.244; 4.O.237.228; 4.O.237.229; 4.O.237.230; 4.O.237.231; 4.O.237.236; 4.O.237.237; 4.O.237.238; 4.O.237.239; 4.O.237.154; 4.O.237.157; 4.O.237.166; 4.O.237.169; 4.O.237.172; 4.O.237.175; 4.O.237.240; 4.O.237.244; 4.O.238.228; 4.O.238.229; 4.O.238.230; 4.O.238.231; 4.O.238.236; 4.O.238.237; 4.O.238.238; 4.O.238.239; 4.O.238.154; 4.O.238.157; 4.O.238.166; 4.O.238.169; 4.O.238.172; 4.O.238.175; 4.O.238.240; 4.O.238.244; 4.O.239.228; 4.O.239.229; 4.O.239.230; 4.O.239.231; 4.O.239.236; 4.O.239.237; 4.O.239.238; 4.O.239.239; 4.O.239.154; 4.O.239.157; 4.O.239.166; 4.O.239.169; 4.O.239.172; 4.O.239.175; 4.O.239.240; 4.O.239.244; 4.O.154.228; 4.O.154.229; 4.O.154.230; 4.O.154.231; 4.O.154.236; 4.O.154.237; 4.O.154.238; 4.O.154.239; 4.O.154.154; 4.O.154.157; 4.O.154.166; 4.O.154.169; 4.O.154.172; 4.O.154.175; 4.O.154.240; 4.O.154.244; 4.O.157.228; 4.O.157.229; 4.O.157.230; 4.O.157.231; 4.O.157.236; 4.O.157.237; 4.O.157.238; 4.O.157.239; 4.O.157.154; 4.O.157.157; 4.O.157.166; 4.O.157.169; 4.O.157.172; 4.O.157.175; 4.O.157.240; 4.O.157.244; 4.O.166.228; 4.O.166.229; 4.O.166.230; 4.O.166.231; 4.O.166.236; 4.O.166.237; 4.O.166.238; 4.O.166.239; 4.O.166.154; 4.O.166.157; 4.O.166.166; 4.O.166.169; 4.O.166.172; 4.O.166.175; 4.O.166.240; 4.O.166.244; 4.O.169.228; 4.O.169.229; 4.O.169.230; 4.O.169.231; 4.O.169.236; 4.O.169.237; 4.O.169.238; 4.O.169.239; 4.O.169.154; 4.O.169.157; 4.O.169.166; 4.O.169.169; 4.O.169.172; 4.O.169.175; 4.O.169.240; 4.O.169.244; 4.O.172.228; 4.O.172.229; 4.O.172.230; 4.O.172.231; 4.O.172.236; 4.O.172.237;

4.O.172.238; 4.O.172.239; 4.O.172.154; 4.O.172.157; 4.O.172.166; 4.O.172.169; 4.O.172.172; 4.O.172.175; 4.O.172.240; 4.O.172.244; 4.O.175.228; 4.O.175.229; 4.O.175.230; 4.O.175.231; 4.O.175.236; 4.O.175.237; 4.O.175.238; 4.O.175.239; 4.O.175.154; 4.O.175.157; 4.O.175.166; 4.O.175.169; 4.O.175.172; 4.O.175.175; 4.O.175.240; 4.O.175.244; 4.O.240.228; 4.O.240.229; 4.O.240.230; 4.O.240.231; 4.O.240.236; 4.O.240.237; 4.O.240.238; 4.O.240.239; 4.O.240.154; 4.O.240.157; 4.O.240.166; 4.O.240.169; 4.O.240.172; 4.O.240.175; 4.O.240.240; 4.O.240.244; 4.O.244.228; 4.O.244.229; 4.O.244.230; 4.O.244.231; 4.O.244.236; 4.O.244.237; 4.O.244.238; 4.O.244.239; 4.O.244.154; 4.O.244.157; 4.O.244.166; 4.O.244.169; 4.O.244.172; 4.O.244.175; 4.O.244.240; 4.O.244.244;

Prodrugs of 4.P

4.P.228.228; 4.P.228.229; 4.P.228.230; 4.P.228.231; 4.P.228.236; 4.P.228.237; 4.P.228.238; 4.P.228.239; 4.P.228.154; 4.P.228.157; 4.P.228.166; 4.P.228.169; 4.P.228.172; 4.P.228.175; 4.P.228.240; 4.P.228.244; 4.P.229.228; 4.P.229.229; 4.P.229.230; 4.P.229.231; 4.P.229.236; 4.P.229.237; 4.P.229.238; 4.P.229.239; 4.P.229.154; 4.P.229.157; 4.P.229.166; 4.P.229.169; 4.P.229.172; 4.P.229.175; 4.P.229.240; 4.P.229.244; 4.P.230.228; 4.P.230.229; 4.P.230.230; 4.P.230.231; 4.P.230.236; 4.P.230.237; 4.P.230.238; 4.P.230.239; 4.P.230.154; 4.P.230.157; 4.P.230.166; 4.P.230.169; 4.P.230.172; 4.P.230.175; 4.P.230.240; 4.P.230.244; 4.P.231.228; 4.P.231.229; 4.P.231.230; 4.P.231.231; 4.P.231.236; 4.P.231.237; 4.P.231.238; 4.P.231.239; 4.P.231.154; 4.P.231.157; 4.P.231.166; 4.P.231.169; 4.P.231.172; 4.P.231.175; 4.P.231.240; 4.P.231.244; 4.P.236.228; 4.P.236.229; 4.P.236.230; 4.P.236.231; 4.P.236.236; 4.P.236.237; 4.P.236.238; 4.P.236.239; 4.P.236.154; 4.P.236.157; 4.P.236.166; 4.P.236.169; 4.P.236.172; 4.P.236.175; 4.P.236.240; 4.P.236.244; 4.P.237.228; 4.P.237.229; 4.P.237.230; 4.P.237.231; 4.P.237.236; 4.P.237.237; 4.P.237.238; 4.P.237.239; 4.P.237.154; 4.P.237.157; 4.P.237.166; 4.P.237.169; 4.P.237.172; 4.P.237.175; 4.P.237.240; 4.P.237.244; 4.P.238.228; 4.P.238.229; 4.P.238.230; 4.P.238.231; 4.P.238.236; 4.P.238.237; 4.P.238.238; 4.P.238.239; 4.P.238.154; 4.P.238.157; 4.P.238.166; 4.P.238.169; 4.P.238.172; 4.P.238.175; 4.P.238.240; 4.P.238.244; 4.P.239.228; 4.P.239.229; 4.P.239.230; 4.P.239.231; 4.P.239.236; 4.P.239.237; 4.P.239.238; 4.P.239.239; 4.P.239.154; 4.P.239.157; 4.P.239.166; 4.P.239.169; 4.P.239.172; 4.P.239.175; 4.P.239.240; 4.P.239.244; 4.P.154.228; 4.P.154.229; 4.P.154.230; 4.P.154.231; 4.P.154.236; 4.P.154.237; 4.P.154.238; 4.P.154.239; 4.P.154.154; 4.P.154.157; 4.P.154.166; 4.P.154.169; 4.P.154.172; 4.P.154.175; 4.P.154.240; 4.P.154.244; 4.P.157.228; 4.P.157.229; 4.P.157.230; 4.P.157.231; 4.P.157.236; 4.P.157.237; 4.P.157.238; 4.P.157.239; 4.P.157.154; 4.P.157.157; 4.P.157.166; 4.P.157.169; 4.P.157.172; 4.P.157.175; 4.P.157.240; 4.P.157.244; 4.P.166.228; 4.P.166.229; 4.P.166.230; 4.P.166.231; 4.P.166.236; 4.P.166.237; 4.P.166.238; 4.P.166.239; 4.P.166.154; 4.P.166.157; 4.P.166.166; 4.P.166.169; 4.P.166.172; 4.P.166.175; 4.P.166.240; 4.P.166.244; 4.P.169.228; 4.P.169.229; 4.P.169.230; 4.P.169.231; 4.P.169.236; 4.P.169.237; 4.P.169.238; 4.P.169.239; 4.P.169.154; 4.P.169.157; 4.P.169.166; 4.P.169.169; 4.P.169.172; 4.P.169.175; 4.P.169.240; 4.P.169.244; 4.P.172.228; 4.P.172.229; 4.P.172.230; 4.P.172.231; 4.P.172.236; 4.P.172.237; 4.P.172.238; 4.P.172.239; 4.P.172.154; 4.P.172.157; 4.P.172.166; 4.P.172.169; 4.P.172.172; 4.P.172.175; 4.P.172.240; 4.P.172.244; 4.P.175.228; 4.P.175.229; 4.P.175.230; 4.P.175.231; 4.P.175.236; 4.P.175.237; 4.P.175.238; 4.P.175.239; 4.P.175.154; 4.P.175.157; 4.P.175.166; 4.P.175.169; 4.P.175.172; 4.P.175.175; 4.P.175.240; 4.P.175.244; 4.P.240.228; 4.P.240.229; 4.P.240.230; 4.P.240.231; 4.P.240.236; 4.P.240.237; 4.P.240.238; 4.P.240.239; 4.P.240.154; 4.P.240.157; 4.P.240.166; 4.P.240.169; 4.P.240.172;

4.P.240.175; 4.P.240.240; 4.P.240.244; 4.P.244.228; 4.P.244.229; 4.P.244.230; 4.P.244.231; 4.P.244.236; 4.P.244.237; 4.P.244.238; 4.P.244.239; 4.P.244.154; 4.P.244.157; 4.P.244.166; 4.P.244.169; 4.P.244.172; 4.P.244.175; 4.P.244.240; 4.P.244.244;

Prodrugs of 4.U

4.U.228.228; 4.U.228.229; 4.U.228.230; 4.U.228.231; 4.U.228.236; 4.U.228.237; 4.U.228.238; 4.U.228.239; 4.U.228.154; 4.U.228.157; 4.U.228.166; 4.U.228.169; 4.U.228.172; 4.U.228.175; 4.U.228.240; 4.U.228.244; 4.U.229.228; 4.U.229.229; 4.U.229.230; 4.U.229.231; 4.U.229.236; 4.U.229.237; 4.U.229.238; 4.U.229.239; 4.U.229.154; 4.U.229.157; 4.U.229.166; 4.U.229.169; 4.U.229.172; 4.U.229.175; 4.U.229.240; 4.U.229.244; 4.U.230.228; 4.U.230.229; 4.U.230.230; 4.U.230.231; 4.U.230.236; 4.U.230.237; 4.U.230.238; 4.U.230.239; 4.U.230.154; 4.U.230.157; 4.U.230.166; 4.U.230.169; 4.U.230.172; 4.U.230.175; 4.U.230.240; 4.U.230.244; 4.U.231.228; 4.U.231.229; 4.U.231.230; 4.U.231.231; 4.U.231.236; 4.U.231.237; 4.U.231.238; 4.U.231.239; 4.U.231.154; 4.U.231.157; 4.U.231.166; 4.U.231.169; 4.U.231.172; 4.U.231.175; 4.U.231.240; 4.U.231.244; 4.U.236.228; 4.U.236.229; 4.U.236.230; 4.U.236.231; 4.U.236.236; 4.U.236.237; 4.U.236.238; 4.U.236.239; 4.U.236.154; 4.U.236.157; 4.U.236.166; 4.U.236.169; 4.U.236.172; 4.U.236.175; 4.U.236.240; 4.U.236.244; 4.U.237.228; 4.U.237.229; 4.U.237.230; 4.U.237.231; 4.U.237.236; 4.U.237.237; 4.U.237.238; 4.U.237.239; 4.U.237.154; 4.U.237.157; 4.U.237.166; 4.U.237.169; 4.U.237.172; 4.U.237.175; 4.U.237.240; 4.U.237.244; 4.U.238.228; 4.U.238.229; 4.U.238.230; 4.U.238.231; 4.U.238.236; 4.U.238.237; 4.U.238.238; 4.U.238.239; 4.U.238.154; 4.U.238.157; 4.U.238.166; 4.U.238.169; 4.U.238.172; 4.U.238.175; 4.U.238.240; 4.U.238.244; 4.U.239.228; 4.U.239.229; 4.U.239.230; 4.U.239.231; 4.U.239.236; 4.U.239.237; 4.U.239.238; 4.U.239.239; 4.U.239.154; 4.U.239.157; 4.U.239.166; 4.U.239.169; 4.U.239.172; 4.U.239.175; 4.U.239.240; 4.U.239.244; 4.U.154.228; 4.U.154.229; 4.U.154.230; 4.U.154.231; 4.U.154.236; 4.U.154.237; 4.U.154.238; 4.U.154.239; 4.U.154.154; 4.U.154.157; 4.U.154.166; 4.U.154.169; 4.U.154.172; 4.U.154.175; 4.U.154.240; 4.U.154.244; 4.U.157.228; 4.U.157.229; 4.U.157.230; 4.U.157.231; 4.U.157.236; 4.U.157.237; 4.U.157.238; 4.U.157.239; 4.U.157.154; 4.U.157.157; 4.U.157.166; 4.U.157.169; 4.U.157.172; 4.U.157.175; 4.U.157.240; 4.U.157.244; 4.U.166.228; 4.U.166.229; 4.U.166.230; 4.U.166.231; 4.U.166.236; 4.U.166.237; 4.U.166.238; 4.U.166.239; 4.U.166.154; 4.U.166.157; 4.U.166.166; 4.U.166.169; 4.U.166.172; 4.U.166.175; 4.U.166.240; 4.U.166.244; 4.U.169.228; 4.U.169.229; 4.U.169.230; 4.U.169.231; 4.U.169.236; 4.U.169.237; 4.U.169.238; 4.U.169.239; 4.U.169.154; 4.U.169.157; 4.U.169.166; 4.U.169.169; 4.U.169.172; 4.U.169.175; 4.U.169.240; 4.U.169.244; 4.U.172.228; 4.U.172.229; 4.U.172.230; 4.U.172.231; 4.U.172.236; 4.U.172.237; 4.U.172.238; 4.U.172.239; 4.U.172.154; 4.U.172.157; 4.U.172.166; 4.U.172.169; 4.U.172.172; 4.U.172.175; 4.U.172.240; 4.U.172.244; 4.U.175.228; 4.U.175.229; 4.U.175.230; 4.U.175.231; 4.U.175.236; 4.U.175.237; 4.U.175.238; 4.U.175.239; 4.U.175.154; 4.U.175.157; 4.U.175.166; 4.U.175.169; 4.U.175.172; 4.U.175.175; 4.U.175.240; 4.U.175.244; 4.U.240.228; 4.U.240.229; 4.U.240.230; 4.U.240.231; 4.U.240.236; 4.U.240.237; 4.U.240.238; 4.U.240.239; 4.U.240.154; 4.U.240.157; 4.U.240.166; 4.U.240.169; 4.U.240.172; 4.U.240.175; 4.U.240.240; 4.U.240.244; 4.U.244.228; 4.U.244.229; 4.U.244.230; 4.U.244.231; 4.U.244.236; 4.U.244.237;

4.U.244.238; 4.U.244.239; 4.U.244.154; 4.U.244.157; 4.U.244.166; 4.U.244.169; 4.U.244.172; 4.U.244.175; 4.U.244.240; 4.U.244.244;

Prodrugs of 4.W

4.W.228.228; 4.W.228.229; 4.W.228.230; 4.W.228.231; 4.W.228.236; 4.W.228.237; 4.W.228.238; 4.W.228.239; 4.W.228.154; 4.W.228.157; 4.W.228.166; 4.W.228.169; 4.W.228.172; 4.W.228.175; 4.W.228.240; 4.W.228.244; 4.W.229.228; 4.W.229.229; 4.W.229.230; 4.W.229.231; 4.W.229.236; 4.W.229.237; 4.W.229.238; 4.W.229.239; 4.W.229.154; 4.W.229.157; 4.W.229.166; 4.W.229.169; 4.W.229.172; 4.W.229.175; 4.W.229.240; 4.W.229.244; 4.W.230.228; 4.W.230.229; 4.W.230.230; 4.W.230.231; 4.W.230.236; 4.W.230.237; 4.W.230.238; 4.W.230.239; 4.W.230.154; 4.W.230.157; 4.W.230.166; 4.W.230.169; 4.W.230.172; 4.W.230.175; 4.W.230.240; 4.W.230.244; 4.W.231.228; 4.W.231.229; 4.W.231.230; 4.W.231.231; 4.W.231.236; 4.W.231.237; 4.W.231.238; 4.W.231.239; 4.W.231.154; 4.W.231.157; 4.W.231.166; 4.W.231.169; 4.W.231.172; 4.W.231.175; 4.W.231.240; 4.W.231.244; 4.W.236.228; 4.W.236.229; 4.W.236.230; 4.W.236.231; 4.W.236.236; 4.W.236.237; 4.W.236.238; 4.W.236.239; 4.W.236.154; 4.W.236.157; 4.W.236.166; 4.W.236.169; 4.W.236.172; 4.W.236.175; 4.W.236.240; 4.W.236.244; 4.W.237.228; 4.W.237.229; 4.W.237.230; 4.W.237.231; 4.W.237.236; 4.W.237.237; 4.W.237.238; 4.W.237.239; 4.W.237.154; 4.W.237.157; 4.W.237.166; 4.W.237.169; 4.W.237.172; 4.W.237.175; 4.W.237.240; 4.W.237.244; 4.W.238.228; 4.W.238.229; 4.W.238.230; 4.W.238.231; 4.W.238.236; 4.W.238.237; 4.W.238.238; 4.W.238.239; 4.W.238.154; 4.W.238.157; 4.W.238.166; 4.W.238.169; 4.W.238.172; 4.W.238.175; 4.W.238.240; 4.W.238.244; 4.W.239.228; 4.W.239.229; 4.W.239.230; 4.W.239.231; 4.W.239.236; 4.W.239.237; 4.W.239.238; 4.W.239.239; 4.W.239.154; 4.W.239.157; 4.W.239.166; 4.W.239.169; 4.W.239.172; 4.W.239.175; 4.W.239.240; 4.W.239.244; 4.W.154.228; 4.W.154.229; 4.W.154.230; 4.W.154.231; 4.W.154.236; 4.W.154.237; 4.W.154.238; 4.W.154.239; 4.W.154.154; 4.W.154.157; 4.W.154.166; 4.W.154.169; 4.W.154.172; 4.W.154.175; 4.W.154.240; 4.W.154.244; 4.W.157.228; 4.W.157.229; 4.W.157.230; 4.W.157.231; 4.W.157.236; 4.W.157.237; 4.W.157.238; 4.W.157.239; 4.W.157.154; 4.W.157.157; 4.W.157.166; 4.W.157.169; 4.W.157.172; 4.W.157.175; 4.W.157.240; 4.W.157.244; 4.W.166.228; 4.W.166.229; 4.W.166.230; 4.W.166.231; 4.W.166.236; 4.W.166.237; 4.W.166.238; 4.W.166.239; 4.W.166.154; 4.W.166.157; 4.W.166.166; 4.W.166.169; 4.W.166.172; 4.W.166.175; 4.W.166.240; 4.W.166.244; 4.W.169.228; 4.W.169.229; 4.W.169.230; 4.W.169.231; 4.W.169.236; 4.W.169.237; 4.W.169.238; 4.W.169.239; 4.W.169.154; 4.W.169.157; 4.W.169.166; 4.W.169.169; 4.W.169.172; 4.W.169.175; 4.W.169.240; 4.W.169.244; 4.W.172.228; 4.W.172.229; 4.W.172.230; 4.W.172.231; 4.W.172.236; 4.W.172.237; 4.W.172.238; 4.W.172.239; 4.W.172.154; 4.W.172.157; 4.W.172.166; 4.W.172.169; 4.W.172.172; 4.W.172.175; 4.W.172.240; 4.W.172.244; 4.W.175.228; 4.W.175.229; 4.W.175.230; 4.W.175.231; 4.W.175.236; 4.W.175.237; 4.W.175.238; 4.W.175.239; 4.W.175.154; 4.W.175.157; 4.W.175.166; 4.W.175.169; 4.W.175.172; 4.W.175.175; 4.W.175.240; 4.W.175.244; 4.W.240.228; 4.W.240.229; 4.W.240.230; 4.W.240.231; 4.W.240.236; 4.W.240.237; 4.W.240.238; 4.W.240.239; 4.W.240.154; 4.W.240.157; 4.W.240.166; 4.W.240.169; 4.W.240.172; 4.W.240.175; 4.W.240.240; 4.W.240.244; 4.W.244.228; 4.W.244.229; 4.W.244.230; 4.W.244.231; 4.W.244.236; 4.W.244.237;

4.W.244.238; 4.W.244.239; 4.W.244.154; 4.W.244.157; 4.W.244.166; 4.W.244.169; 4.W.244.172; 4.W.244.175; 4.W.244.240; 4.W.244.244;

Prodrugs of 4.Y

4.Y.228.228; 4.Y.228.229; 4.Y.228.230; 4.Y.228.231; 4.Y.228.236; 4.Y.228.237; 4.Y.228.238; 4.Y.228.239; 4.Y.228.154; 4.Y.228.157; 4.Y.228.166; 4.Y.228.169; 4.Y.228.172; 4.Y.228.175; 4.Y.228.240; 4.Y.228.244; 4.Y.229.228; 4.Y.229.229; 4.Y.229.230; 4.Y.229.231; 4.Y.229.236; 4.Y.229.237; 4.Y.229.238; 4.Y.229.239; 4.Y.229.154; 4.Y.229.157; 4.Y.229.166; 4.Y.229.169; 4.Y.229.172; 4.Y.229.175; 4.Y.229.240; 4.Y.229.244; 4.Y.230.228; 4.Y.230.229; 4.Y.230.230; 4.Y.230.231; 4.Y.230.236; 4.Y.230.237; 4.Y.230.238; 4.Y.230.239; 4.Y.230.154; 4.Y.230.157; 4.Y.230.166; 4.Y.230.169; 4.Y.230.172; 4.Y.230.175; 4.Y.230.240; 4.Y.230.244; 4.Y.231.228; 4.Y.231.229; 4.Y.231.230; 4.Y.231.231; 4.Y.231.236; 4.Y.231.237; 4.Y.231.238; 4.Y.231.239; 4.Y.231.154; 4.Y.231.157; 4.Y.231.166; 4.Y.231.169; 4.Y.231.172; 4.Y.231.175; 4.Y.231.240; 4.Y.231.244; 4.Y.236.228; 4.Y.236.229; 4.Y.236.230; 4.Y.236.231; 4.Y.236.236; 4.Y.236.237; 4.Y.236.238; 4.Y.236.239; 4.Y.236.154; 4.Y.236.157; 4.Y.236.166; 4.Y.236.169; 4.Y.236.172; 4.Y.236.175; 4.Y.236.240; 4.Y.236.244; 4.Y.237.228; 4.Y.237.229; 4.Y.237.230; 4.Y.237.231; 4.Y.237.236; 4.Y.237.237; 4.Y.237.238; 4.Y.237.239; 4.Y.237.154; 4.Y.237.157; 4.Y.237.166; 4.Y.237.169; 4.Y.237.172; 4.Y.237.175; 4.Y.237.240; 4.Y.237.244; 4.Y.238.228; 4.Y.238.229; 4.Y.238.230; 4.Y.238.231; 4.Y.238.236; 4.Y.238.237; 4.Y.238.238; 4.Y.238.239; 4.Y.238.154; 4.Y.238.157; 4.Y.238.166; 4.Y.238.169; 4.Y.238.172; 4.Y.238.175; 4.Y.238.240; 4.Y.238.244; 4.Y.239.228; 4.Y.239.229; 4.Y.239.230; 4.Y.239.231; 4.Y.239.236; 4.Y.239.237; 4.Y.239.238; 4.Y.239.239; 4.Y.239.154; 4.Y.239.157; 4.Y.239.166; 4.Y.239.169; 4.Y.239.172; 4.Y.239.175; 4.Y.239.240; 4.Y.239.244; 4.Y.154.228; 4.Y.154.229; 4.Y.154.230; 4.Y.154.231; 4.Y.154.236; 4.Y.154.237; 4.Y.154.238; 4.Y.154.239; 4.Y.154.154; 4.Y.154.157; 4.Y.154.166; 4.Y.154.169; 4.Y.154.172; 4.Y.154.175; 4.Y.154.240; 4.Y.154.244; 4.Y.157.228; 4.Y.157.229; 4.Y.157.230; 4.Y.157.231; 4.Y.157.236; 4.Y.157.237; 4.Y.157.238; 4.Y.157.239; 4.Y.157.154; 4.Y.157.157; 4.Y.157.166; 4.Y.157.169; 4.Y.157.172; 4.Y.157.175; 4.Y.157.240; 4.Y.157.244; 4.Y.166.228; 4.Y.166.229; 4.Y.166.230; 4.Y.166.231; 4.Y.166.236; 4.Y.166.237; 4.Y.166.238; 4.Y.166.239; 4.Y.166.154; 4.Y.166.157; 4.Y.166.166; 4.Y.166.169; 4.Y.166.172; 4.Y.166.175; 4.Y.166.240; 4.Y.166.244; 4.Y.169.228; 4.Y.169.229; 4.Y.169.230; 4.Y.169.231; 4.Y.169.236; 4.Y.169.237; 4.Y.169.238; 4.Y.169.239; 4.Y.169.154; 4.Y.169.157; 4.Y.169.166; 4.Y.169.169; 4.Y.169.172; 4.Y.169.175; 4.Y.169.240; 4.Y.169.244; 4.Y.172.228; 4.Y.172.229; 4.Y.172.230; 4.Y.172.231; 4.Y.172.236; 4.Y.172.237; 4.Y.172.238; 4.Y.172.239; 4.Y.172.154; 4.Y.172.157; 4.Y.172.166; 4.Y.172.169; 4.Y.172.172; 4.Y.172.175; 4.Y.172.240; 4.Y.172.244; 4.Y.175.228; 4.Y.175.229; 4.Y.175.230; 4.Y.175.231; 4.Y.175.236; 4.Y.175.237; 4.Y.175.238; 4.Y.175.239; 4.Y.175.154; 4.Y.175.157; 4.Y.175.166; 4.Y.175.169; 4.Y.175.172; 4.Y.175.175; 4.Y.175.240; 4.Y.175.244; 4.Y.240.228; 4.Y.240.229; 4.Y.240.230; 4.Y.240.231; 4.Y.240.236; 4.Y.240.237; 4.Y.240.238; 4.Y.240.239; 4.Y.240.154; 4.Y.240.157; 4.Y.240.166; 4.Y.240.169; 4.Y.240.172; 4.Y.240.175; 4.Y.240.240; 4.Y.240.244; 4.Y.244.228; 4.Y.244.229; 4.Y.244.230; 4.Y.244.231; 4.Y.244.236; 4.Y.244.237;

4.Y.244.238; 4.Y.244.239; 4.Y.244.154; 4.Y.244.157; 4.Y.244.166; 4.Y.244.169; 4.Y.244.172; 4.Y.244.175; 4.Y.244.240; 4.Y.244.244;

Prodrugs of 5.B

5.B.228.228; 5.B.228.229; 5.B.228.230; 5.B.228.231; 5.B.228.236; 5.B.228.237; 5.B.228.238; 5.B.228.239; 5.B.228.154; 5.B.228.157; 5.B.228.166; 5.B.228.169; 5.B.228.172; 5.B.228.175; 5.B.228.240; 5.B.228.244; 5.B.229.228; 5.B.229.229; 5.B.229.230; 5.B.229.231; 5.B.229.236; 5.B.229.237; 5.B.229.238; 5.B.229.239; 5.B.229.154; 5.B.229.157; 5.B.229.166; 5.B.229.169; 5.B.229.172; 5.B.229.175; 5.B.229.240; 5.B.229.244; 5.B.230.228; 5.B.230.229; 5.B.230.230; 5.B.230.231; 5.B.230.236; 5.B.230.237; 5.B.230.238; 5.B.230.239; 5.B.230.154; 5.B.230.157; 5.B.230.166; 5.B.230.169; 5.B.230.172; 5.B.230.175; 5.B.230.240; 5.B.230.244; 5.B.231.228; 5.B.231.229; 5.B.231.230; 5.B.231.231; 5.B.231.236; 5.B.231.237; 5.B.231.238; 5.B.231.239; 5.B.231.154; 5.B.231.157; 5.B.231.166; 5.B.231.169; 5.B.231.172; 5.B.231.175; 5.B.231.240; 5.B.231.244; 5.B.236.228; 5.B.236.229; 5.B.236.230; 5.B.236.231; 5.B.236.236; 5.B.236.237; 5.B.236.238; 5.B.236.239; 5.B.236.154; 5.B.236.157; 5.B.236.166; 5.B.236.169; 5.B.236.172; 5.B.236.175; 5.B.236.240; 5.B.236.244; 5.B.237.228; 5.B.237.229; 5.B.237.230; 5.B.237.231; 5.B.237.236; 5.B.237.237; 5.B.237.238; 5.B.237.239; 5.B.237.154; 5.B.237.157; 5.B.237.166; 5.B.237.169; 5.B.237.172; 5.B.237.175; 5.B.237.240; 5.B.237.244; 5.B.238.228; 5.B.238.229; 5.B.238.230; 5.B.238.231; 5.B.238.236; 5.B.238.237; 5.B.238.238; 5.B.238.239; 5.B.238.154; 5.B.238.157; 5.B.238.166; 5.B.238.169; 5.B.238.172; 5.B.238.175; 5.B.238.240; 5.B.238.244; 5.B.239.228; 5.B.239.229; 5.B.239.230; 5.B.239.231; 5.B.239.236; 5.B.239.237; 5.B.239.238; 5.B.239.239; 5.B.239.154; 5.B.239.157; 5.B.239.166; 5.B.239.169; 5.B.239.172; 5.B.239.175; 5.B.239.240; 5.B.239.244; 5.B.154.228; 5.B.154.229; 5.B.154.230; 5.B.154.231; 5.B.154.236; 5.B.154.237; 5.B.154.238; 5.B.154.239; 5.B.154.154; 5.B.154.157; 5.B.154.166; 5.B.154.169; 5.B.154.172; 5.B.154.175; 5.B.154.240; 5.B.154.244; 5.B.157.228; 5.B.157.229; 5.B.157.230; 5.B.157.231; 5.B.157.236; 5.B.157.237; 5.B.157.238; 5.B.157.239; 5.B.157.154; 5.B.157.157; 5.B.157.166; 5.B.157.169; 5.B.157.172; 5.B.157.175; 5.B.157.240; 5.B.157.244; 5.B.166.228; 5.B.166.229; 5.B.166.230; 5.B.166.231; 5.B.166.236; 5.B.166.237; 5.B.166.238; 5.B.166.239; 5.B.166.154; 5.B.166.157; 5.B.166.166; 5.B.166.169; 5.B.166.172; 5.B.166.175; 5.B.166.240; 5.B.166.244; 5.B.169.228; 5.B.169.229; 5.B.169.230; 5.B.169.231; 5.B.169.236; 5.B.169.237; 5.B.169.238; 5.B.169.239; 5.B.169.154; 5.B.169.157; 5.B.169.166; 5.B.169.169; 5.B.169.172; 5.B.169.175; 5.B.169.240; 5.B.169.244; 5.B.172.228; 5.B.172.229; 5.B.172.230; 5.B.172.231; 5.B.172.236; 5.B.172.237; 5.B.172.238; 5.B.172.239; 5.B.172.154; 5.B.172.157; 5.B.172.166; 5.B.172.169; 5.B.172.172; 5.B.172.175; 5.B.172.240; 5.B.172.244; 5.B.175.228; 5.B.175.229; 5.B.175.230; 5.B.175.231; 5.B.175.236; 5.B.175.237; 5.B.175.238; 5.B.175.239; 5.B.175.154; 5.B.175.157; 5.B.175.166; 5.B.175.169; 5.B.175.172; 5.B.175.175; 5.B.175.240; 5.B.175.244; 5.B.240.228; 5.B.240.229; 5.B.240.230; 5.B.240.231; 5.B.240.236; 5.B.240.237; 5.B.240.238; 5.B.240.239; 5.B.240.154; 5.B.240.157; 5.B.240.166; 5.B.240.169; 5.B.240.172; 5.B.240.175; 5.B.240.240; 5.B.240.244; 5.B.244.228; 5.B.244.229; 5.B.244.230; 5.B.244.231; 5.B.244.236; 5.B.244.237; 5.B.244.238; 5.B.244.239; 5.B.244.154; 5.B.244.157; 5.B.244.166; 5.B.244.169; 5.B.244.172; 5.B.244.175; 5.B.244.240; 5.B.244.244;

Prodrugs of 5.D

5.D.228.228; 5.D.228.229; 5.D.228.230; 5.D.228.231; 5.D.228.236; 5.D.228.237; 5.D.228.238; 5.D.228.239; 5.D.228.154; 5.D.228.157; 5.D.228.166; 5.D.228.169; 5.D.228.172; 5.D.228.175; 5.D.228.240; 5.D.228.244; 5.D.229.228; 5.D.229.229;

5.D.229.230; 5.D.229.231; 5.D.229.236; 5.D.229.237; 5.D.229.238; 5.D.229.239; 5.D.229.154; 5.D.229.157; 5.D.229.166; 5.D.229.169; 5.D.229.172; 5.D.229.175; 5.D.229.240; 5.D.229.244; 5.D.230.228; 5.D.230.229; 5.D.230.230; 5.D.230.231; 5.D.230.236; 5.D.230.237; 5.D.230.238; 5.D.230.239; 5.D.230.154; 5.D.230.157; 5.D.230.166; 5.D.230.169; 5.D.230.172; 5.D.230.175; 5.D.230.240; 5.D.230.244; 5.D.231.228; 5.D.231.229; 5.D.231.230; 5.D.231.231; 5.D.231.236; 5.D.231.237; 5.D.231.238; 5.D.231.239; 5.D.231.154; 5.D.231.157; 5.D.231.166; 5.D.231.169; 5.D.231.172; 5.D.231.175; 5.D.231.240; 5.D.231.244; 5.D.236.228; 5.D.236.229; 5.D.236.230; 5.D.236.231; 5.D.236.236; 5.D.236.237; 5.D.236.238; 5.D.236.239; 5.D.236.154; 5.D.236.157; 5.D.236.166; 5.D.236.169; 5.D.236.172; 5.D.236.175; 5.D.236.240; 5.D.236.244; 5.D.237.228; 5.D.237.229; 5.D.237.230; 5.D.237.231; 5.D.237.236; 5.D.237.237; 5.D.237.238; 5.D.237.239; 5.D.237.154; 5.D.237.157; 5.D.237.166; 5.D.237.169; 5.D.237.172; 5.D.237.175; 5.D.237.240; 5.D.237.244; 5.D.238.228; 5.D.238.229; 5.D.238.230; 5.D.238.231; 5.D.238.236; 5.D.238.237; 5.D.238.238; 5.D.238.239; 5.D.238.154; 5.D.238.157; 5.D.238.166; 5.D.238.169; 5.D.238.172; 5.D.238.175; 5.D.238.240; 5.D.238.244; 5.D.239.228; 5.D.239.229; 5.D.239.230; 5.D.239.231; 5.D.239.236; 5.D.239.237; 5.D.239.238; 5.D.239.239; 5.D.239.154; 5.D.239.157; 5.D.239.166; 5.D.239.169; 5.D.239.172; 5.D.239.175; 5.D.239.240; 5.D.239.244; 5.D.154.228; 5.D.154.229; 5.D.154.230; 5.D.154.231; 5.D.154.236; 5.D.154.237; 5.D.154.238; 5.D.154.239; 5.D.154.154; 5.D.154.157; 5.D.154.166; 5.D.154.169; 5.D.154.172; 5.D.154.175; 5.D.154.240; 5.D.154.244; 5.D.157.228; 5.D.157.229; 5.D.157.230; 5.D.157.231; 5.D.157.236; 5.D.157.237; 5.D.157.238; 5.D.157.239; 5.D.157.154; 5.D.157.157; 5.D.157.166; 5.D.157.169; 5.D.157.172; 5.D.157.175; 5.D.157.240; 5.D.157.244; 5.D.166.228; 5.D.166.229; 5.D.166.230; 5.D.166.231; 5.D.166.236; 5.D.166.237; 5.D.166.238; 5.D.166.239; 5.D.166.154; 5.D.166.157; 5.D.166.166; 5.D.166.169; 5.D.166.172; 5.D.166.175; 5.D.166.240; 5.D.166.244; 5.D.169.228; 5.D.169.229; 5.D.169.230; 5.D.169.231; 5.D.169.236; 5.D.169.237; 5.D.169.238; 5.D.169.239; 5.D.169.154; 5.D.169.157; 5.D.169.166; 5.D.169.169; 5.D.169.172; 5.D.169.175; 5.D.169.240; 5.D.169.244; 5.D.172.228; 5.D.172.229; 5.D.172.230; 5.D.172.231; 5.D.172.236; 5.D.172.237; 5.D.172.238; 5.D.172.239; 5.D.172.154; 5.D.172.157; 5.D.172.166; 5.D.172.169; 5.D.172.172; 5.D.172.175; 5.D.172.240; 5.D.172.244; 5.D.175.228; 5.D.175.229; 5.D.175.230; 5.D.175.231; 5.D.175.236; 5.D.175.237; 5.D.175.238; 5.D.175.239; 5.D.175.154; 5.D.175.157; 5.D.175.166; 5.D.175.169; 5.D.175.172; 5.D.175.175; 5.D.175.240; 5.D.175.244; 5.D.240.228; 5.D.240.229; 5.D.240.230; 5.D.240.231; 5.D.240.236; 5.D.240.237; 5.D.240.238; 5.D.240.239; 5.D.240.154; 5.D.240.157; 5.D.240.166; 5.D.240.169; 5.D.240.172; 5.D.240.175; 5.D.240.240; 5.D.240.244; 5.D.244.228; 5.D.244.229; 5.D.244.230; 5.D.244.231; 5.D.244.236; 5.D.244.237; 5.D.244.238; 5.D.244.239; 5.D.244.154; 5.D.244.157; 5.D.244.166; 5.D.244.169; 5.D.244.172; 5.D.244.175; 5.D.244.240; 5.D.244.244;

<u>Prodrugs of 5.E</u>

5.E.228.228; 5.E.228.229; 5.E.228.230; 5.E.228.231; 5.E.228.236; 5.E.228.237; 5.E.228.238; 5.E.228.239; 5.E.228.154; 5.E.228.157; 5.E.228.166; 5.E.228.169; 5.E.228.172; 5.E.228.175; 5.E.228.240; 5.E.228.244; 5.E.229.228; 5.E.229.229; 5.E.229.230; 5.E.229.231; 5.E.229.236; 5.E.229.237; 5.E.229.238; 5.E.229.239; 5.E.229.154; 5.E.229.157; 5.E.229.166;

5.E.229.169; 5.E.229.172; 5.E.229.175; 5.E.229.240; 5.E.229.244; 5.E.230.228; 5.E.230.229; 5.E.230.230; 5.E.230.231; 5.E.230.236; 5.E.230.237; 5.E.230.238; 5.E.230.239; 5.E.230.154; 5.E.230.157; 5.E.230.166; 5.E.230.169; 5.E.230.172; 5.E.230.175; 5.E.230.240; 5.E.230.244; 5.E.231.228; 5.E.231.229; 5.E.231.230; 5.E.231.231; 5.E.231.236; 5.E.231.237; 5.E.231.238; 5.E.231.239; 5.E.231.154; 5.E.231.157; 5.E.231.166; 5.E.231.169; 5.E.231.172; 5.E.231.175; 5.E.231.240; 5.E.231.244; 5.E.236.228; 5.E.236.229; 5.E.236.230; 5.E.236.231; 5.E.236.236; 5.E.236.237; 5.E.236.238; 5.E.236.239; 5.E.236.154; 5.E.236.157; 5.E.236.166; 5.E.236.169; 5.E.236.172; 5.E.236.175; 5.E.236.240; 5.E.236.244; 5.E.237.228; 5.E.237.229; 5.E.237.230; 5.E.237.231; 5.E.237.236; 5.E.237.237; 5.E.237.238; 5.E.237.239; 5.E.237.154; 5.E.237.157; 5.E.237.166; 5.E.237.169; 5.E.237.172; 5.E.237.175; 5.E.237.240; 5.E.237.244; 5.E.238.228; 5.E.238.229; 5.E.238.230; 5.E.238.231; 5.E.238.236; 5.E.238.237; 5.E.238.238; 5.E.238.239; 5.E.238.154; 5.E.238.157; 5.E.238.166; 5.E.238.169; 5.E.238.172; 5.E.238.175; 5.E.238.240; 5.E.238.244; 5.E.239.228; 5.E.239.229; 5.E.239.230; 5.E.239.231; 5.E.239.236; 5.E.239.237; 5.E.239.238; 5.E.239.239; 5.E.239.154; 5.E.239.157; 5.E.239.166; 5.E.239.169; 5.E.239.172; 5.E.239.175; 5.E.239.240; 5.E.239.244; 5.E.154.228; 5.E.154.229; 5.E.154.230; 5.E.154.231; 5.E.154.236; 5.E.154.237; 5.E.154.238; 5.E.154.239; 5.E.154.154; 5.E.154.157; 5.E.154.166; 5.E.154.169; 5.E.154.172; 5.E.154.175; 5.E.154.240; 5.E.154.244; 5.E.157.228; 5.E.157.229; 5.E.157.230; 5.E.157.231; 5.E.157.236; 5.E.157.237; 5.E.157.238; 5.E.157.239; 5.E.157.154; 5.E.157.157; 5.E.157.166; 5.E.157.169; 5.E.157.172; 5.E.157.175; 5.E.157.240; 5.E.157.244; 5.E.166.228; 5.E.166.229; 5.E.166.230; 5.E.166.231; 5.E.166.236; 5.E.166.237; 5.E.166.238; 5.E.166.239; 5.E.166.154; 5.E.166.157; 5.E.166.166; 5.E.166.169; 5.E.166.172; 5.E.166.175; 5.E.166.240; 5.E.166.244; 5.E.169.228; 5.E.169.229; 5.E.169.230; 5.E.169.231; 5.E.169.236; 5.E.169.237; 5.E.169.238; 5.E.169.239; 5.E.169.154; 5.E.169.157; 5.E.169.166; 5.E.169.169; 5.E.169.172; 5.E.169.175; 5.E.169.240; 5.E.169.244; 5.E.172.228; 5.E.172.229; 5.E.172.230; 5.E.172.231; 5.E.172.236; 5.E.172.237; 5.E.172.238; 5.E.172.239; 5.E.172.154; 5.E.172.157; 5.E.172.166; 5.E.172.169; 5.E.172.172; 5.E.172.175; 5.E.172.240; 5.E.172.244; 5.E.175.228; 5.E.175.229; 5.E.175.230; 5.E.175.231; 5.E.175.236; 5.E.175.237; 5.E.175.238; 5.E.175.239; 5.E.175.154; 5.E.175.157; 5.E.175.166; 5.E.175.169; 5.E.175.172; 5.E.175.175; 5.E.175.240; 5.E.175.244; 5.E.240.228; 5.E.240.229; 5.E.240.230; 5.E.240.231; 5.E.240.236; 5.E.240.237; 5.E.240.238; 5.E.240.239; 5.E.240.154; 5.E.240.157; 5.E.240.166; 5.E.240.169; 5.E.240.172; 5.E.240.175; 5.E.240.240; 5.E.240.244; 5.E.244.228; 5.E.244.229; 5.E.244.230; 5.E.244.231; 5.E.244.236; 5.E.244.237; 5.E.244.238; 5.E.244.239; 5.E.244.154; 5.E.244.157; 5.E.244.166; 5.E.244.169; 5.E.244.172; 5.E.244.175; 5.E.244.240; 5.E.244.244;

<u>Prodrugs of 5.G</u>

5.G.228.228; 5.G.228.229; 5.G.228.230; 5.G.228.231; 5.G.228.236; 5.G.228.237; 5.G.228.238; 5.G.228.239; 5.G.228.154; 5.G.228.157; 5.G.228.166; 5.G.228.169; 5.G.228.172; 5.G.228.175; 5.G.228.240; 5.G.228.244; 5.G.229.228; 5.G.229.229; 5.G.229.230; 5.G.229.231; 5.G.229.236; 5.G.229.237; 5.G.229.238; 5.G.229.239; 5.G.229.154; 5.G.229.157; 5.G.229.166; 5.G.229.169; 5.G.229.172; 5.G.229.175; 5.G.229.240; 5.G.229.244; 5.G.230.228; 5.G.230.229; 5.G.230.230; 5.G.230.231; 5.G.230.236; 5.G.230.237; 5.G.230.238; 5.G.230.239; 5.G.230.154; 5.G.230.157; 5.G.230.166; 5.G.230.169; 5.G.230.172; 5.G.230.175; 5.G.230.240; 5.G.230.244; 5.G.231.228; 5.G.231.229; 5.G.231.230; 5.G.231.231; 5.G.231.236; 5.G.231.237; 5.G.231.238; 5.G.231.239; 5.G.231.154; 5.G.231.157; 5.G.231.166; 5.G.231.169; 5.G.231.172; 5.G.231.175; 5.G.231.240; 5.G.231.244; 5.G.236.228; 5.G.236.229;

5.G.236.230; 5.G.236.231; 5.G.236.236; 5.G.236.237; 5.G.236.238; 5.G.236.239; 5.G.236.154; 5.G.236.157; 5.G.236.166; 5.G.236.169; 5.G.236.172; 5.G.236.175; 5.G.236.240; 5.G.236.244; 5.G.237.228; 5.G.237.229; 5.G.237.230; 5.G.237.231; 5.G.237.236; 5.G.237.237; 5.G.237.238; 5.G.237.239; 5.G.237.154; 5.G.237.157; 5.G.237.166; 5.G.237.169; 5.G.237.172; 5.G.237.175; 5.G.237.240; 5.G.237.244; 5.G.238.228; 5.G.238.229; 5.G.238.230; 5.G.238.231; 5.G.238.236; 5.G.238.237; 5.G.238.238; 5.G.238.239; 5.G.238.154; 5.G.238.157; 5.G.238.166; 5.G.238.169; 5.G.238.172; 5.G.238.175; 5.G.238.240; 5.G.238.244; 5.G.239.228; 5.G.239.229; 5.G.239.230; 5.G.239.231; 5.G.239.236; 5.G.239.237; 5.G.239.238; 5.G.239.239; 5.G.239.154; 5.G.239.157; 5.G.239.166; 5.G.239.169; 5.G.239.172; 5.G.239.175; 5.G.239.240; 5.G.239.244; 5.G.154.228; 5.G.154.229; 5.G.154.230; 5.G.154.231; 5.G.154.236; 5.G.154.237; 5.G.154.238; 5.G.154.239; 5.G.154.154; 5.G.154.157; 5.G.154.166; 5.G.154.169; 5.G.154.172; 5.G.154.175; 5.G.154.240; 5.G.154.244; 5.G.157.228; 5.G.157.229; 5.G.157.230; 5.G.157.231; 5.G.157.236; 5.G.157.237; 5.G.157.238; 5.G.157.239; 5.G.157.154; 5.G.157.157; 5.G.157.166; 5.G.157.169; 5.G.157.172; 5.G.157.175; 5.G.157.240; 5.G.157.244; 5.G.166.228; 5.G.166.229; 5.G.166.230; 5.G.166.231; 5.G.166.236; 5.G.166.237; 5.G.166.238; 5.G.166.239; 5.G.166.154; 5.G.166.157; 5.G.166.166; 5.G.166.169; 5.G.166.172; 5.G.166.175; 5.G.166.240; 5.G.166.244; 5.G.169.228; 5.G.169.229; 5.G.169.230; 5.G.169.231; 5.G.169.236; 5.G.169.237; 5.G.169.238; 5.G.169.239; 5.G.169.154; 5.G.169.157; 5.G.169.166; 5.G.169.169; 5.G.169.172; 5.G.169.175; 5.G.169.240; 5.G.169.244; 5.G.172.228; 5.G.172.229; 5.G.172.230; 5.G.172.231; 5.G.172.236; 5.G.172.237; 5.G.172.238; 5.G.172.239; 5.G.172.154; 5.G.172.157; 5.G.172.166; 5.G.172.169; 5.G.172.172; 5.G.172.175; 5.G.172.240; 5.G.172.244; 5.G.175.228; 5.G.175.229; 5.G.175.230; 5.G.175.231; 5.G.175.236; 5.G.175.237; 5.G.175.238; 5.G.175.239; 5.G.175.154; 5.G.175.157; 5.G.175.166; 5.G.175.169; 5.G.175.172; 5.G.175.175; 5.G.175.240; 5.G.175.244; 5.G.240.228; 5.G.240.229; 5.G.240.230; 5.G.240.231; 5.G.240.236; 5.G.240.237; 5.G.240.238; 5.G.240.239; 5.G.240.154; 5.G.240.157; 5.G.240.166; 5.G.240.169; 5.G.240.172; 5.G.240.175; 5.G.240.240; 5.G.240.244; 5.G.244.228; 5.G.244.229; 5.G.244.230; 5.G.244.231; 5.G.244.236; 5.G.244.237; 5.G.244.238; 5.G.244.239; 5.G.244.154; 5.G.244.157; 5.G.244.166; 5.G.244.169; 5.G.244.172; 5.G.244.175; 5.G.244.240; 5.G.244.244;

Prodrugs of 5.I

5.I.228.228; 5.I.228.229; 5.I.228.230; 5.I.228.231; 5.I.228.236; 5.I.228.237; 5.I.228.238; 5.I.228.239; 5.I.228.154; 5.I.228.157; 5.I.228.166; 5.I.228.169; 5.I.228.172; 5.I.228.175; 5.I.228.240; 5.I.228.244; 5.I.229.228; 5.I.229.229; 5.I.229.230; 5.I.229.231; 5.I.229.236; 5.I.229.237; 5.I.229.238; 5.I.229.239; 5.I.229.154; 5.I.229.157; 5.I.229.166; 5.I.229.169; 5.I.229.172; 5.I.229.175; 5.I.229.240; 5.I.229.244; 5.I.230.228; 5.I.230.229; 5.I.230.230; 5.I.230.231; 5.I.230.236; 5.I.230.237; 5.I.230.238; 5.I.230.239; 5.I.230.154; 5.I.230.157; 5.I.230.166; 5.I.230.169; 5.I.230.172; 5.I.230.175; 5.I.230.240; 5.I.230.244; 5.I.231.228; 5.I.231.229; 5.I.231.230; 5.I.231.231; 5.I.231.236; 5.I.231.237; 5.I.231.238; 5.I.231.239; 5.I.231.154; 5.I.231.157; 5.I.231.166; 5.I.231.169; 5.I.231.172; 5.I.231.175; 5.I.231.240; 5.I.231.244; 5.I.236.228; 5.I.236.229; 5.I.236.230; 5.I.236.231; 5.I.236.236; 5.I.236.237; 5.I.236.238; 5.I.236.239; 5.I.236.154; 5.I.236.157; 5.I.236.166; 5.I.236.169; 5.I.236.172; 5.I.236.175; 5.I.236.240; 5.I.236.244; 5.I.237.228; 5.I.237.229; 5.I.237.230; 5.I.237.231;

5.I.237.236; 5.I.237.237; 5.I.237.238; 5.I.237.239; 5.I.237.154; 5.I.237.157; 5.I.237.166; 5.I.237.169; 5.I.237.172; 5.I.237.175; 5.I.237.240; 5.I.237.244; 5.I.238.228; 5.I.238.229; 5.I.238.230; 5.I.238.231; 5.I.238.236; 5.I.238.237; 5.I.238.238; 5.I.238.239; 5.I.238.154; 5.I.238.157; 5.I.238.166; 5.I.238.169; 5.I.238.172; 5.I.238.175; 5.I.238.240; 5.I.238.244; 5.I.239.228; 5.I.239.229; 5.I.239.230; 5.I.239.231; 5.I.239.236; 5.I.239.237; 5.I.239.238; 5.I.239.239; 5.I.239.154; 5.I.239.157; 5.I.239.166; 5.I.239.169; 5.I.239.172; 5.I.239.175; 5.I.239.240; 5.I.239.244; 5.I.154.228; 5.I.154.229; 5.I.154.230; 5.I.154.231; 5.I.154.236; 5.I.154.237; 5.I.154.238; 5.I.154.239; 5.I.154.154; 5.I.154.157; 5.I.154.166; 5.I.154.169; 5.I.154.172; 5.I.154.175; 5.I.154.240; 5.I.154.244; 5.I.157.228; 5.I.157.229; 5.I.157.230; 5.I.157.231; 5.I.157.236; 5.I.157.237; 5.I.157.238; 5.I.157.239; 5.I.157.154; 5.I.157.157; 5.I.157.166; 5.I.157.169; 5.I.157.172; 5.I.157.175; 5.I.157.240; 5.I.157.244; 5.I.166.228; 5.I.166.229; 5.I.166.230; 5.I.166.231; 5.I.166.236; 5.I.166.237; 5.I.166.238; 5.I.166.239; 5.I.166.154; 5.I.166.157; 5.I.166.166; 5.I.166.169; 5.I.166.172; 5.I.166.175; 5.I.166.240; 5.I.166.244; 5.I.169.228; 5.I.169.229; 5.I.169.230; 5.I.169.231; 5.I.169.236; 5.I.169.237; 5.I.169.238; 5.I.169.239; 5.I.169.154; 5.I.169.157; 5.I.169.166; 5.I.169.169; 5.I.169.172; 5.I.169.175; 5.I.169.240; 5.I.169.244; 5.I.172.228; 5.I.172.229; 5.I.172.230; 5.I.172.231; 5.I.172.236; 5.I.172.237; 5.I.172.238; 5.I.172.239; 5.I.172.154; 5.I.172.157; 5.I.172.166; 5.I.172.169; 5.I.172.172; 5.I.172.175; 5.I.172.240; 5.I.172.244; 5.I.175.228; 5.I.175.229; 5.I.175.230; 5.I.175.231; 5.I.175.236; 5.I.175.237; 5.I.175.238; 5.I.175.239; 5.I.175.154; 5.I.175.157; 5.I.175.166; 5.I.175.169; 5.I.175.172; 5.I.175.175; 5.I.175.240; 5.I.175.244; 5.I.240.228; 5.I.240.229; 5.I.240.230; 5.I.240.231; 5.I.240.236; 5.I.240.237; 5.I.240.238; 5.I.240.239; 5.I.240.154; 5.I.240.157; 5.I.240.166; 5.I.240.169; 5.I.240.172; 5.I.240.175; 5.I.240.240; 5.I.240.244; 5.I.244.228; 5.I.244.229; 5.I.244.230; 5.I.244.231; 5.I.244.236; 5.I.244.237; 5.I.244.238; 5.I.244.239; 5.I.244.154; 5.I.244.157; 5.I.244.166; 5.I.244.169; 5.I.244.172; 5.I.244.175; 5.I.244.240; 5.I.244.244;

Prodrugs of 5.J

5.J.228.228; 5.J.228.229; 5.J.228.230; 5.J.228.231; 5.J.228.236; 5.J.228.237; 5.J.228.238; 5.J.228.239; 5.J.228.154; 5.J.228.157; 5.J.228.166; 5.J.228.169; 5.J.228.172; 5.J.228.175; 5.J.228.240; 5.J.228.244; 5.J.229.228; 5.J.229.229; 5.J.229.230; 5.J.229.231; 5.J.229.236; 5.J.229.237; 5.J.229.238; 5.J.229.239; 5.J.229.154; 5.J.229.157; 5.J.229.166; 5.J.229.169; 5.J.229.172; 5.J.229.175; 5.J.229.240; 5.J.229.244; 5.J.230.228; 5.J.230.229; 5.J.230.230; 5.J.230.231; 5.J.230.236; 5.J.230.237; 5.J.230.238; 5.J.230.239; 5.J.230.154; 5.J.230.157; 5.J.230.166; 5.J.230.169; 5.J.230.172; 5.J.230.175; 5.J.230.240; 5.J.230.244; 5.J.231.228; 5.J.231.229; 5.J.231.230; 5.J.231.231; 5.J.231.236; 5.J.231.237; 5.J.231.238; 5.J.231.239; 5.J.231.154; 5.J.231.157; 5.J.231.166; 5.J.231.169; 5.J.231.172; 5.J.231.175; 5.J.231.240; 5.J.231.244; 5.J.236.228; 5.J.236.229; 5.J.236.230; 5.J.236.231; 5.J.236.236; 5.J.236.237; 5.J.236.238; 5.J.236.239; 5.J.236.154; 5.J.236.157; 5.J.236.166; 5.J.236.169; 5.J.236.172; 5.J.236.175; 5.J.236.240; 5.J.236.244; 5.J.237.228; 5.J.237.229; 5.J.237.230; 5.J.237.231; 5.J.237.236; 5.J.237.237; 5.J.237.238; 5.J.237.239; 5.J.237.154; 5.J.237.157; 5.J.237.166; 5.J.237.169; 5.J.237.172; 5.J.237.175; 5.J.237.240; 5.J.237.244; 5.J.238.228; 5.J.238.229; 5.J.238.230; 5.J.238.231; 5.J.238.236; 5.J.238.237; 5.J.238.238; 5.J.238.239; 5.J.238.154; 5.J.238.157; 5.J.238.166; 5.J.238.169; 5.J.238.172; 5.J.238.175; 5.J.238.240; 5.J.238.244; 5.J.239.228; 5.J.239.229; 5.J.239.230; 5.J.239.231; 5.J.239.236; 5.J.239.237; 5.J.239.238; 5.J.239.239; 5.J.239.154; 5.J.239.157; 5.J.239.166; 5.J.239.169; 5.J.239.172; 5.J.239.175; 5.J.239.240; 5.J.239.244; 5.J.154.228; 5.J.154.229; 5.J.154.230; 5.J.154.231; 5.J.154.236;

5.J.154.237; 5.J.154.238; 5.J.154.239; 5.J.154.154; 5.J.154.157; 5.J.154.166; 5.J.154.169; 5.J.154.172; 5.J.154.175; 5.J.154.240; 5.J.154.244; 5.J.157.228; 5.J.157.229; 5.J.157.230; 5.J.157.231; 5.J.157.236; 5.J.157.237; 5.J.157.238; 5.J.157.239; 5.J.157.154; 5.J.157.157; 5.J.157.166; 5.J.157.169; 5.J.157.172; 5.J.157.175; 5.J.157.240; 5.J.157.244; 5.J.166.228; 5.J.166.229; 5.J.166.230; 5.J.166.231; 5.J.166.236; 5.J.166.237; 5.J.166.238; 5.J.166.239; 5.J.166.154; 5.J.166.157; 5.J.166.166; 5.J.166.169; 5.J.166.172; 5.J.166.175; 5.J.166.240; 5.J.166.244; 5.J.169.228; 5.J.169.229; 5.J.169.230; 5.J.169.231; 5.J.169.236; 5.J.169.237; 5.J.169.238; 5.J.169.239; 5.J.169.154; 5.J.169.157; 5.J.169.166; 5.J.169.169; 5.J.169.172; 5.J.169.175; 5.J.169.240; 5.J.169.244; 5.J.172.228; 5.J.172.229; 5.J.172.230; 5.J.172.231; 5.J.172.236; 5.J.172.237; 5.J.172.238; 5.J.172.239; 5.J.172.154; 5.J.172.157; 5.J.172.166; 5.J.172.169; 5.J.172.172; 5.J.172.175; 5.J.172.240; 5.J.172.244; 5.J.175.228; 5.J.175.229; 5.J.175.230; 5.J.175.231; 5.J.175.236; 5.J.175.237; 5.J.175.238; 5.J.175.239; 5.J.175.154; 5.J.175.157; 5.J.175.166; 5.J.175.169; 5.J.175.172; 5.J.175.175; 5.J.175.240; 5.J.175.244; 5.J.240.228; 5.J.240.229; 5.J.240.230; 5.J.240.231; 5.J.240.236; 5.J.240.237; 5.J.240.238; 5.J.240.239; 5.J.240.154; 5.J.240.157; 5.J.240.166; 5.J.240.169; 5.J.240.172; 5.J.240.175; 5.J.240.240; 5.J.240.244; 5.J.244.228; 5.J.244.229; 5.J.244.230; 5.J.244.231; 5.J.244.236; 5.J.244.237; 5.J.244.238; 5.J.244.239; 5.J.244.154; 5.J.244.157; 5.J.244.166; 5.J.244.169; 5.J.244.172; 5.J.244.175; 5.J.244.240; 5.J.244.244;

Prodrugs of 5.L

5.L.228.228; 5.L.228.229; 5.L.228.230; 5.L.228.231; 5.L.228.236; 5.L.228.237; 5.L.228.238; 5.L.228.239; 5.L.228.154; 5.L.228.157; 5.L.228.166; 5.L.228.169; 5.L.228.172; 5.L.228.175; 5.L.228.240; 5.L.228.244; 5.L.229.228; 5.L.229.229; 5.L.229.230; 5.L.229.231; 5.L.229.236; 5.L.229.237; 5.L.229.238; 5.L.229.239; 5.L.229.154; 5.L.229.157; 5.L.229.166; 5.L.229.169; 5.L.229.172; 5.L.229.175; 5.L.229.240; 5.L.229.244; 5.L.230.228; 5.L.230.229; 5.L.230.230; 5.L.230.231; 5.L.230.236; 5.L.230.237; 5.L.230.238; 5.L.230.239; 5.L.230.154; 5.L.230.157; 5.L.230.166; 5.L.230.169; 5.L.230.172; 5.L.230.175; 5.L.230.240; 5.L.230.244; 5.L.231.228; 5.L.231.229; 5.L.231.230; 5.L.231.231; 5.L.231.236; 5.L.231.237; 5.L.231.238; 5.L.231.239; 5.L.231.154; 5.L.231.157; 5.L.231.166; 5.L.231.169; 5.L.231.172; 5.L.231.175; 5.L.231.240; 5.L.231.244; 5.L.236.228; 5.L.236.229; 5.L.236.230; 5.L.236.231; 5.L.236.236; 5.L.236.237; 5.L.236.238; 5.L.236.239; 5.L.236.154; 5.L.236.157; 5.L.236.166; 5.L.236.169; 5.L.236.172; 5.L.236.175; 5.L.236.240; 5.L.236.244; 5.L.237.228; 5.L.237.229; 5.L.237.230; 5.L.237.231; 5.L.237.236; 5.L.237.237; 5.L.237.238; 5.L.237.239; 5.L.237.154; 5.L.237.157; 5.L.237.166; 5.L.237.169; 5.L.237.172; 5.L.237.175; 5.L.237.240; 5.L.237.244; 5.L.238.228; 5.L.238.229; 5.L.238.230; 5.L.238.231; 5.L.238.236; 5.L.238.237; 5.L.238.238; 5.L.238.239; 5.L.238.154; 5.L.238.157; 5.L.238.166; 5.L.238.169; 5.L.238.172; 5.L.238.175; 5.L.238.240; 5.L.238.244; 5.L.239.228; 5.L.239.229; 5.L.239.230; 5.L.239.231; 5.L.239.236; 5.L.239.237; 5.L.239.238; 5.L.239.239; 5.L.239.154; 5.L.239.157; 5.L.239.166; 5.L.239.169; 5.L.239.172; 5.L.239.175; 5.L.239.240; 5.L.239.244; 5.L.154.228; 5.L.154.229; 5.L.154.230; 5.L.154.231; 5.L.154.236; 5.L.154.237; 5.L.154.238; 5.L.154.239; 5.L.154.154; 5.L.154.157; 5.L.154.166; 5.L.154.169; 5.L.154.172; 5.L.154.175; 5.L.154.240; 5.L.154.244; 5.L.157.228; 5.L.157.229; 5.L.157.230; 5.L.157.231; 5.L.157.236; 5.L.157.237; 5.L.157.238; 5.L.157.239; 5.L.157.154; 5.L.157.157; 5.L.157.166; 5.L.157.169; 5.L.157.172; 5.L.157.175; 5.L.157.240; 5.L.157.244; 5.L.166.228; 5.L.166.229; 5.L.166.230; 5.L.166.231; 5.L.166.236; 5.L.166.237; 5.L.166.238; 5.L.166.239; 5.L.166.154; 5.L.166.157; 5.L.166.166; 5.L.166.169; 5.L.166.172; 5.L.166.175; 5.L.166.240; 5.L.166.244; 5.L.169.228; 5.L.169.229; 5.L.169.230; 5.L.169.231; 5.L.169.236;

5.L.169.237; 5.L.169.238; 5.L.169.239; 5.L.169.154; 5.L.169.157; 5.L.169.166; 5.L.169.169; 5.L.169.172; 5.L.169.175; 5.L.169.240; 5.L.169.244; 5.L.172.228; 5.L.172.229; 5.L.172.230; 5.L.172.231; 5.L.172.236; 5.L.172.237; 5.L.172.238; 5.L.172.239; 5.L.172.154; 5.L.172.157; 5.L.172.166; 5.L.172.169; 5.L.172.172; 5.L.172.175; 5.L.172.240; 5.L.172.244; 5.L.175.228; 5.L.175.229; 5.L.175.230; 5.L.175.231; 5.L.175.236; 5.L.175.237; 5.L.175.238; 5.L.175.239; 5.L.175.154; 5.L.175.157; 5.L.175.166; 5.L.175.169; 5.L.175.172; 5.L.175.175; 5.L.175.240; 5.L.175.244; 5.L.240.228; 5.L.240.229; 5.L.240.230; 5.L.240.231; 5.L.240.236; 5.L.240.237; 5.L.240.238; 5.L.240.239; 5.L.240.154; 5.L.240.157; 5.L.240.166; 5.L.240.169; 5.L.240.172; 5.L.240.175; 5.L.240.240; 5.L.240.244; 5.L.244.228; 5.L.244.229; 5.L.244.230; 5.L.244.231; 5.L.244.236; 5.L.244.237; 5.L.244.238; 5.L.244.239; 5.L.244.154; 5.L.244.157; 5.L.244.166; 5.L.244.169; 5.L.244.172; 5.L.244.175; 5.L.244.240; 5.L.244.244;

<u>Prodrugs of 5.O</u>

5.O.228.228; 5.O.228.229; 5.O.228.230; 5.O.228.231; 5.O.228.236; 5.O.228.237; 5.O.228.238; 5.O.228.239; 5.O.228.154; 5.O.228.157; 5.O.228.166; 5.O.228.169; 5.O.228.172; 5.O.228.175; 5.O.228.240; 5.O.228.244; 5.O.229.228; 5.O.229.229; 5.O.229.230; 5.O.229.231; 5.O.229.236; 5.O.229.237; 5.O.229.238; 5.O.229.239; 5.O.229.154; 5.O.229.157; 5.O.229.166; 5.O.229.169; 5.O.229.172; 5.O.229.175; 5.O.229.240; 5.O.229.244; 5.O.230.228; 5.O.230.229; 5.O.230.230; 5.O.230.231; 5.O.230.236; 5.O.230.237; 5.O.230.238; 5.O.230.239; 5.O.230.154; 5.O.230.157; 5.O.230.166; 5.O.230.169; 5.O.230.172; 5.O.230.175; 5.O.230.240; 5.O.230.244; 5.O.231.228; 5.O.231.229; 5.O.231.230; 5.O.231.231; 5.O.231.236; 5.O.231.237; 5.O.231.238; 5.O.231.239; 5.O.231.154; 5.O.231.157; 5.O.231.166; 5.O.231.169; 5.O.231.172; 5.O.231.175; 5.O.231.240; 5.O.231.244; 5.O.236.228; 5.O.236.229; 5.O.236.230; 5.O.236.231; 5.O.236.236; 5.O.236.237; 5.O.236.238; 5.O.236.239; 5.O.236.154; 5.O.236.157; 5.O.236.166; 5.O.236.169; 5.O.236.172; 5.O.236.175; 5.O.236.240; 5.O.236.244; 5.O.237.228; 5.O.237.229; 5.O.237.230; 5.O.237.231; 5.O.237.236; 5.O.237.237; 5.O.237.238; 5.O.237.239; 5.O.237.154; 5.O.237.157; 5.O.237.166; 5.O.237.169; 5.O.237.172; 5.O.237.175; 5.O.237.240; 5.O.237.244; 5.O.238.228; 5.O.238.229; 5.O.238.230; 5.O.238.231; 5.O.238.236; 5.O.238.237; 5.O.238.238; 5.O.238.239; 5.O.238.154; 5.O.238.157; 5.O.238.166; 5.O.238.169; 5.O.238.172; 5.O.238.175; 5.O.238.240; 5.O.238.244; 5.O.239.228; 5.O.239.229; 5.O.239.230; 5.O.239.231; 5.O.239.236; 5.O.239.237; 5.O.239.238; 5.O.239.239; 5.O.239.154; 5.O.239.157; 5.O.239.166; 5.O.239.169; 5.O.239.172; 5.O.239.175; 5.O.239.240; 5.O.239.244; 5.O.154.228; 5.O.154.229; 5.O.154.230; 5.O.154.231; 5.O.154.236; 5.O.154.237; 5.O.154.238; 5.O.154.239; 5.O.154.154; 5.O.154.157; 5.O.154.166; 5.O.154.169; 5.O.154.172; 5.O.154.175; 5.O.154.240; 5.O.154.244; 5.O.157.228; 5.O.157.229; 5.O.157.230; 5.O.157.231; 5.O.157.236; 5.O.157.237; 5.O.157.238; 5.O.157.239; 5.O.157.154; 5.O.157.157; 5.O.157.166; 5.O.157.169; 5.O.157.172; 5.O.157.175; 5.O.157.240; 5.O.157.244; 5.O.166.228; 5.O.166.229; 5.O.166.230; 5.O.166.231; 5.O.166.236; 5.O.166.237; 5.O.166.238; 5.O.166.239; 5.O.166.154; 5.O.166.157; 5.O.166.166; 5.O.166.169; 5.O.166.172; 5.O.166.175; 5.O.166.240; 5.O.166.244; 5.O.169.228; 5.O.169.229; 5.O.169.230; 5.O.169.231; 5.O.169.236; 5.O.169.237; 5.O.169.238; 5.O.169.239; 5.O.169.154; 5.O.169.157; 5.O.169.166; 5.O.169.169; 5.O.169.172; 5.O.169.175; 5.O.169.240; 5.O.169.244; 5.O.172.228; 5.O.172.229; 5.O.172.230; 5.O.172.231; 5.O.172.236; 5.O.172.237;

5.O.172.238; 5.O.172.239; 5.O.172.154; 5.O.172.157; 5.O.172.166; 5.O.172.169; 5.O.172.172; 5.O.172.175; 5.O.172.240; 5.O.172.244; 5.O.175.228; 5.O.175.229; 5.O.175.230; 5.O.175.231; 5.O.175.236; 5.O.175.237; 5.O.175.238; 5.O.175.239; 5.O.175.154; 5.O.175.157; 5.O.175.166; 5.O.175.169; 5.O.175.172; 5.O.175.175; 5.O.175.240; 5.O.175.244; 5.O.240.228; 5.O.240.229; 5.O.240.230; 5.O.240.231; 5.O.240.236; 5.O.240.237; 5.O.240.238; 5.O.240.239; 5.O.240.154; 5.O.240.157; 5.O.240.166; 5.O.240.169; 5.O.240.172; 5.O.240.175; 5.O.240.240; 5.O.240.244; 5.O.244.228; 5.O.244.229; 5.O.244.230; 5.O.244.231; 5.O.244.236; 5.O.244.237; 5.O.244.238; 5.O.244.239; 5.O.244.154; 5.O.244.157; 5.O.244.166; 5.O.244.169; 5.O.244.172; 5.O.244.175; 5.O.244.240; 5.O.244.244;

Prodrugs of 5.P

5.P.228.228; 5.P.228.229; 5.P.228.230; 5.P.228.231; 5.P.228.236; 5.P.228.237; 5.P.228.238; 5.P.228.239; 5.P.228.154; 5.P.228.157; 5.P.228.166; 5.P.228.169; 5.P.228.172; 5.P.228.175; 5.P.228.240; 5.P.228.244; 5.P.229.228; 5.P.229.229; 5.P.229.230; 5.P.229.231; 5.P.229.236; 5.P.229.237; 5.P.229.238; 5.P.229.239; 5.P.229.154; 5.P.229.157; 5.P.229.166; 5.P.229.169; 5.P.229.172; 5.P.229.175; 5.P.229.240; 5.P.229.244; 5.P.230.228; 5.P.230.229; 5.P.230.230; 5.P.230.231; 5.P.230.236; 5.P.230.237; 5.P.230.238; 5.P.230.239; 5.P.230.154; 5.P.230.157; 5.P.230.166; 5.P.230.169; 5.P.230.172; 5.P.230.175; 5.P.230.240; 5.P.230.244; 5.P.231.228; 5.P.231.229; 5.P.231.230; 5.P.231.231; 5.P.231.236; 5.P.231.237; 5.P.231.238; 5.P.231.239; 5.P.231.154; 5.P.231.157; 5.P.231.166; 5.P.231.169; 5.P.231.172; 5.P.231.175; 5.P.231.240; 5.P.231.244; 5.P.236.228; 5.P.236.229; 5.P.236.230; 5.P.236.231; 5.P.236.236; 5.P.236.237; 5.P.236.238; 5.P.236.239; 5.P.236.154; 5.P.236.157; 5.P.236.166; 5.P.236.169; 5.P.236.172; 5.P.236.175; 5.P.236.240; 5.P.236.244; 5.P.237.228; 5.P.237.229; 5.P.237.230; 5.P.237.231; 5.P.237.236; 5.P.237.237; 5.P.237.238; 5.P.237.239; 5.P.237.154; 5.P.237.157; 5.P.237.166; 5.P.237.169; 5.P.237.172; 5.P.237.175; 5.P.237.240; 5.P.237.244; 5.P.238.228; 5.P.238.229; 5.P.238.230; 5.P.238.231; 5.P.238.236; 5.P.238.237; 5.P.238.238; 5.P.238.239; 5.P.238.154; 5.P.238.157; 5.P.238.166; 5.P.238.169; 5.P.238.172; 5.P.238.175; 5.P.238.240; 5.P.238.244; 5.P.239.228; 5.P.239.229; 5.P.239.230; 5.P.239.231; 5.P.239.236; 5.P.239.237; 5.P.239.238; 5.P.239.239; 5.P.239.154; 5.P.239.157; 5.P.239.166; 5.P.239.169; 5.P.239.172; 5.P.239.175; 5.P.239.240; 5.P.239.244; 5.P.154.228; 5.P.154.229; 5.P.154.230; 5.P.154.231; 5.P.154.236; 5.P.154.237; 5.P.154.238; 5.P.154.239; 5.P.154.154; 5.P.154.157; 5.P.154.166; 5.P.154.169; 5.P.154.172; 5.P.154.175; 5.P.154.240; 5.P.154.244; 5.P.157.228; 5.P.157.229; 5.P.157.230; 5.P.157.231; 5.P.157.236; 5.P.157.237; 5.P.157.238; 5.P.157.239; 5.P.157.154; 5.P.157.157; 5.P.157.166; 5.P.157.169; 5.P.157.172; 5.P.157.175; 5.P.157.240; 5.P.157.244; 5.P.166.228; 5.P.166.229; 5.P.166.230; 5.P.166.231; 5.P.166.236; 5.P.166.237; 5.P.166.238; 5.P.166.239; 5.P.166.154; 5.P.166.157; 5.P.166.166; 5.P.166.169; 5.P.166.172; 5.P.166.175; 5.P.166.240; 5.P.166.244; 5.P.169.228; 5.P.169.229; 5.P.169.230; 5.P.169.231; 5.P.169.236; 5.P.169.237; 5.P.169.238; 5.P.169.239; 5.P.169.154; 5.P.169.157; 5.P.169.166; 5.P.169.169; 5.P.169.172; 5.P.169.175; 5.P.169.240; 5.P.169.244; 5.P.172.228; 5.P.172.229; 5.P.172.230; 5.P.172.231; 5.P.172.236; 5.P.172.237; 5.P.172.238; 5.P.172.239; 5.P.172.154; 5.P.172.157; 5.P.172.166; 5.P.172.169; 5.P.172.172; 5.P.172.175; 5.P.172.240; 5.P.172.244; 5.P.175.228; 5.P.175.229; 5.P.175.230; 5.P.175.231; 5.P.175.236; 5.P.175.237; 5.P.175.238; 5.P.175.239; 5.P.175.154; 5.P.175.157; 5.P.175.166; 5.P.175.169; 5.P.175.172; 5.P.175.175; 5.P.175.240; 5.P.175.244; 5.P.240.228; 5.P.240.229; 5.P.240.230; 5.P.240.231; 5.P.240.236; 5.P.240.237; 5.P.240.238; 5.P.240.239; 5.P.240.154; 5.P.240.157; 5.P.240.166; 5.P.240.169; 5.P.240.172;

5.P.240.175; 5.P.240.240; 5.P.240.244; 5.P.244.228; 5.P.244.229; 5.P.244.230; 5.P.244.231; 5.P.244.236; 5.P.244.237; 5.P.244.238; 5.P.244.239; 5.P.244.154; 5.P.244.157; 5.P.244.166; 5.P.244.169; 5.P.244.172; 5.P.244.175; 5.P.244.240; 5.P.244.244;

Prodrugs of 5.U

5.U.228.228; 5.U.228.229; 5.U.228.230; 5.U.228.231; 5.U.228.236; 5.U.228.237; 5.U.228.238; 5.U.228.239; 5.U.228.154; 5.U.228.157; 5.U.228.166; 5.U.228.169; 5.U.228.172; 5.U.228.175; 5.U.228.240; 5.U.228.244; 5.U.229.228; 5.U.229.229; 5.U.229.230; 5.U.229.231; 5.U.229.236; 5.U.229.237; 5.U.229.238; 5.U.229.239; 5.U.229.154; 5.U.229.157; 5.U.229.166; 5.U.229.169; 5.U.229.172; 5.U.229.175; 5.U.229.240; 5.U.229.244; 5.U.230.228; 5.U.230.229; 5.U.230.230; 5.U.230.231; 5.U.230.236; 5.U.230.237; 5.U.230.238; 5.U.230.239; 5.U.230.154; 5.U.230.157; 5.U.230.166; 5.U.230.169; 5.U.230.172; 5.U.230.175; 5.U.230.240; 5.U.230.244; 5.U.231.228; 5.U.231.229; 5.U.231.230; 5.U.231.231; 5.U.231.236; 5.U.231.237; 5.U.231.238; 5.U.231.239; 5.U.231.154; 5.U.231.157; 5.U.231.166; 5.U.231.169; 5.U.231.172; 5.U.231.175; 5.U.231.240; 5.U.231.244; 5.U.236.228; 5.U.236.229; 5.U.236.230; 5.U.236.231; 5.U.236.236; 5.U.236.237; 5.U.236.238; 5.U.236.239; 5.U.236.154; 5.U.236.157; 5.U.236.166; 5.U.236.169; 5.U.236.172; 5.U.236.175; 5.U.236.240; 5.U.236.244; 5.U.237.228; 5.U.237.229; 5.U.237.230; 5.U.237.231; 5.U.237.236; 5.U.237.237; 5.U.237.238; 5.U.237.239; 5.U.237.154; 5.U.237.157; 5.U.237.166; 5.U.237.169; 5.U.237.172; 5.U.237.175; 5.U.237.240; 5.U.237.244; 5.U.238.228; 5.U.238.229; 5.U.238.230; 5.U.238.231; 5.U.238.236; 5.U.238.237; 5.U.238.238; 5.U.238.239; 5.U.238.154; 5.U.238.157; 5.U.238.166; 5.U.238.169; 5.U.238.172; 5.U.238.175; 5.U.238.240; 5.U.238.244; 5.U.239.228; 5.U.239.229; 5.U.239.230; 5.U.239.231; 5.U.239.236; 5.U.239.237; 5.U.239.238; 5.U.239.239; 5.U.239.154; 5.U.239.157; 5.U.239.166; 5.U.239.169; 5.U.239.172; 5.U.239.175; 5.U.239.240; 5.U.239.244; 5.U.154.228; 5.U.154.229; 5.U.154.230; 5.U.154.231; 5.U.154.236; 5.U.154.237; 5.U.154.238; 5.U.154.239; 5.U.154.154; 5.U.154.157; 5.U.154.166; 5.U.154.169; 5.U.154.172; 5.U.154.175; 5.U.154.240; 5.U.154.244; 5.U.157.228; 5.U.157.229; 5.U.157.230; 5.U.157.231; 5.U.157.236; 5.U.157.237; 5.U.157.238; 5.U.157.239; 5.U.157.154; 5.U.157.157; 5.U.157.166; 5.U.157.169; 5.U.157.172; 5.U.157.175; 5.U.157.240; 5.U.157.244; 5.U.166.228; 5.U.166.229; 5.U.166.230; 5.U.166.231; 5.U.166.236; 5.U.166.237; 5.U.166.238; 5.U.166.239; 5.U.166.154; 5.U.166.157; 5.U.166.166; 5.U.166.169; 5.U.166.172; 5.U.166.175; 5.U.166.240; 5.U.166.244; 5.U.169.228; 5.U.169.229; 5.U.169.230; 5.U.169.231; 5.U.169.236; 5.U.169.237; 5.U.169.238; 5.U.169.239; 5.U.169.154; 5.U.169.157; 5.U.169.166; 5.U.169.169; 5.U.169.172; 5.U.169.175; 5.U.169.240; 5.U.169.244; 5.U.172.228; 5.U.172.229; 5.U.172.230; 5.U.172.231; 5.U.172.236; 5.U.172.237; 5.U.172.238; 5.U.172.239; 5.U.172.154; 5.U.172.157; 5.U.172.166; 5.U.172.169; 5.U.172.172; 5.U.172.175; 5.U.172.240; 5.U.172.244; 5.U.175.228; 5.U.175.229; 5.U.175.230; 5.U.175.231; 5.U.175.236; 5.U.175.237; 5.U.175.238; 5.U.175.239; 5.U.175.154; 5.U.175.157; 5.U.175.166; 5.U.175.169; 5.U.175.172; 5.U.175.175; 5.U.175.240; 5.U.175.244; 5.U.240.228; 5.U.240.229; 5.U.240.230; 5.U.240.231; 5.U.240.236; 5.U.240.237; 5.U.240.238; 5.U.240.239; 5.U.240.154; 5.U.240.157; 5.U.240.166; 5.U.240.169; 5.U.240.172; 5.U.240.175; 5.U.240.240; 5.U.240.244; 5.U.244.228; 5.U.244.229; 5.U.244.230; 5.U.244.231; 5.U.244.236; 5.U.244.237;

5.U.244.238; 5.U.244.239; 5.U.244.154; 5.U.244.157; 5.U.244.166; 5.U.244.169; 5.U.244.172; 5.U.244.175; 5.U.244.240; 5.U.244.244;

Prodrugs of 5.W

5.W.228.228; 5.W.228.229; 5.W.228.230; 5.W.228.231; 5.W.228.236; 5.W.228.237; 5.W.228.238; 5.W.228.239; 5.W.228.154; 5.W.228.157; 5.W.228.166; 5.W.228.169; 5.W.228.172; 5.W.228.175; 5.W.228.240; 5.W.228.244; 5.W.229.228; 5.W.229.229; 5.W.229.230; 5.W.229.231; 5.W.229.236; 5.W.229.237; 5.W.229.238; 5.W.229.239; 5.W.229.154; 5.W.229.157; 5.W.229.166; 5.W.229.169; 5.W.229.172; 5.W.229.175; 5.W.229.240; 5.W.229.244; 5.W.230.228; 5.W.230.229; 5.W.230.230; 5.W.230.231; 5.W.230.236; 5.W.230.237; 5.W.230.238; 5.W.230.239; 5.W.230.154; 5.W.230.157; 5.W.230.166; 5.W.230.169; 5.W.230.172; 5.W.230.175; 5.W.230.240; 5.W.230.244; 5.W.231.228; 5.W.231.229; 5.W.231.230; 5.W.231.231; 5.W.231.236; 5.W.231.237; 5.W.231.238; 5.W.231.239; 5.W.231.154; 5.W.231.157; 5.W.231.166; 5.W.231.169; 5.W.231.172; 5.W.231.175; 5.W.231.240; 5.W.231.244; 5.W.236.228; 5.W.236.229; 5.W.236.230; 5.W.236.231; 5.W.236.236; 5.W.236.237; 5.W.236.238; 5.W.236.239; 5.W.236.154; 5.W.236.157; 5.W.236.166; 5.W.236.169; 5.W.236.172; 5.W.236.175; 5.W.236.240; 5.W.236.244; 5.W.237.228; 5.W.237.229; 5.W.237.230; 5.W.237.231; 5.W.237.236; 5.W.237.237; 5.W.237.238; 5.W.237.239; 5.W.237.154; 5.W.237.157; 5.W.237.166; 5.W.237.169; 5.W.237.172; 5.W.237.175; 5.W.237.240; 5.W.237.244; 5.W.238.228; 5.W.238.229; 5.W.238.230; 5.W.238.231; 5.W.238.236; 5.W.238.237; 5.W.238.238; 5.W.238.239; 5.W.238.154; 5.W.238.157; 5.W.238.166; 5.W.238.169; 5.W.238.172; 5.W.238.175; 5.W.238.240; 5.W.238.244; 5.W.239.228; 5.W.239.229; 5.W.239.230; 5.W.239.231; 5.W.239.236; 5.W.239.237; 5.W.239.238; 5.W.239.239; 5.W.239.154; 5.W.239.157; 5.W.239.166; 5.W.239.169; 5.W.239.172; 5.W.239.175; 5.W.239.240; 5.W.239.244; 5.W.154.228; 5.W.154.229; 5.W.154.230; 5.W.154.231; 5.W.154.236; 5.W.154.237; 5.W.154.238; 5.W.154.239; 5.W.154.154; 5.W.154.157; 5.W.154.166; 5.W.154.169; 5.W.154.172; 5.W.154.175; 5.W.154.240; 5.W.154.244; 5.W.157.228; 5.W.157.229; 5.W.157.230; 5.W.157.231; 5.W.157.236; 5.W.157.237; 5.W.157.238; 5.W.157.239; 5.W.157.154; 5.W.157.157; 5.W.157.166; 5.W.157.169; 5.W.157.172; 5.W.157.175; 5.W.157.240; 5.W.157.244; 5.W.166.228; 5.W.166.229; 5.W.166.230; 5.W.166.231; 5.W.166.236; 5.W.166.237; 5.W.166.238; 5.W.166.239; 5.W.166.154; 5.W.166.157; 5.W.166.166; 5.W.166.169; 5.W.166.172; 5.W.166.175; 5.W.166.240; 5.W.166.244; 5.W.169.228; 5.W.169.229; 5.W.169.230; 5.W.169.231; 5.W.169.236; 5.W.169.237; 5.W.169.238; 5.W.169.239; 5.W.169.154; 5.W.169.157; 5.W.169.166; 5.W.169.169; 5.W.169.172; 5.W.169.175; 5.W.169.240; 5.W.169.244; 5.W.172.228; 5.W.172.229; 5.W.172.230; 5.W.172.231; 5.W.172.236; 5.W.172.237; 5.W.172.238; 5.W.172.239; 5.W.172.154; 5.W.172.157; 5.W.172.166; 5.W.172.169; 5.W.172.172; 5.W.172.175; 5.W.172.240; 5.W.172.244; 5.W.175.228; 5.W.175.229; 5.W.175.230; 5.W.175.231; 5.W.175.236; 5.W.175.237; 5.W.175.238; 5.W.175.239; 5.W.175.154; 5.W.175.157; 5.W.175.166; 5.W.175.169; 5.W.175.172; 5.W.175.175; 5.W.175.240; 5.W.175.244; 5.W.240.228; 5.W.240.229; 5.W.240.230; 5.W.240.231; 5.W.240.236; 5.W.240.237; 5.W.240.238; 5.W.240.239; 5.W.240.154; 5.W.240.157; 5.W.240.166; 5.W.240.169; 5.W.240.172; 5.W.240.175; 5.W.240.240; 5.W.240.244; 5.W.244.228; 5.W.244.229; 5.W.244.230; 5.W.244.231; 5.W.244.236; 5.W.244.237;

5.W.244.238; 5.W.244.239; 5.W.244.154; 5.W.244.157; 5.W.244.166; 5.W.244.169; 5.W.244.172; 5.W.244.175; 5.W.244.240; 5.W.244.244;

Prodrugs of 5.Y

5.Y.228.228; 5.Y.228.229; 5.Y.228.230; 5.Y.228.231; 5.Y.228.236; 5.Y.228.237; 5.Y.228.238; 5.Y.228.239; 5.Y.228.154; 5.Y.228.157; 5.Y.228.166; 5.Y.228.169; 5.Y.228.172; 5.Y.228.175; 5.Y.228.240; 5.Y.228.244; 5.Y.229.228; 5.Y.229.229; 5.Y.229.230; 5.Y.229.231; 5.Y.229.236; 5.Y.229.237; 5.Y.229.238; 5.Y.229.239; 5.Y.229.154; 5.Y.229.157; 5.Y.229.166; 5.Y.229.169; 5.Y.229.172; 5.Y.229.175; 5.Y.229.240; 5.Y.229.244; 5.Y.230.228; 5.Y.230.229; 5.Y.230.230; 5.Y.230.231; 5.Y.230.236; 5.Y.230.237; 5.Y.230.238; 5.Y.230.239; 5.Y.230.154; 5.Y.230.157; 5.Y.230.166; 5.Y.230.169; 5.Y.230.172; 5.Y.230.175; 5.Y.230.240; 5.Y.230.244; 5.Y.231.228; 5.Y.231.229; 5.Y.231.230; 5.Y.231.231; 5.Y.231.236; 5.Y.231.237; 5.Y.231.238; 5.Y.231.239; 5.Y.231.154; 5.Y.231.157; 5.Y.231.166; 5.Y.231.169; 5.Y.231.172; 5.Y.231.175; 5.Y.231.240; 5.Y.231.244; 5.Y.236.228; 5.Y.236.229; 5.Y.236.230; 5.Y.236.231; 5.Y.236.236; 5.Y.236.237; 5.Y.236.238; 5.Y.236.239; 5.Y.236.154; 5.Y.236.157; 5.Y.236.166; 5.Y.236.169; 5.Y.236.172; 5.Y.236.175; 5.Y.236.240; 5.Y.236.244; 5.Y.237.228; 5.Y.237.229; 5.Y.237.230; 5.Y.237.231; 5.Y.237.236; 5.Y.237.237; 5.Y.237.238; 5.Y.237.239; 5.Y.237.154; 5.Y.237.157; 5.Y.237.166; 5.Y.237.169; 5.Y.237.172; 5.Y.237.175; 5.Y.237.240; 5.Y.237.244; 5.Y.238.228; 5.Y.238.229; 5.Y.238.230; 5.Y.238.231; 5.Y.238.236; 5.Y.238.237; 5.Y.238.238; 5.Y.238.239; 5.Y.238.154; 5.Y.238.157; 5.Y.238.166; 5.Y.238.169; 5.Y.238.172; 5.Y.238.175; 5.Y.238.240; 5.Y.238.244; 5.Y.239.228; 5.Y.239.229; 5.Y.239.230; 5.Y.239.231; 5.Y.239.236; 5.Y.239.237; 5.Y.239.238; 5.Y.239.239; 5.Y.239.154; 5.Y.239.157; 5.Y.239.166; 5.Y.239.169; 5.Y.239.172; 5.Y.239.175; 5.Y.239.240; 5.Y.239.244; 5.Y.154.228; 5.Y.154.229; 5.Y.154.230; 5.Y.154.231; 5.Y.154.236; 5.Y.154.237; 5.Y.154.238; 5.Y.154.239; 5.Y.154.154; 5.Y.154.157; 5.Y.154.166; 5.Y.154.169; 5.Y.154.172; 5.Y.154.175; 5.Y.154.240; 5.Y.154.244; 5.Y.157.228; 5.Y.157.229; 5.Y.157.230; 5.Y.157.231; 5.Y.157.236; 5.Y.157.237; 5.Y.157.238; 5.Y.157.239; 5.Y.157.154; 5.Y.157.157; 5.Y.157.166; 5.Y.157.169; 5.Y.157.172; 5.Y.157.175; 5.Y.157.240; 5.Y.157.244; 5.Y.166.228; 5.Y.166.229; 5.Y.166.230; 5.Y.166.231; 5.Y.166.236; 5.Y.166.237; 5.Y.166.238; 5.Y.166.239; 5.Y.166.154; 5.Y.166.157; 5.Y.166.166; 5.Y.166.169; 5.Y.166.172; 5.Y.166.175; 5.Y.166.240; 5.Y.166.244; 5.Y.169.228; 5.Y.169.229; 5.Y.169.230; 5.Y.169.231; 5.Y.169.236; 5.Y.169.237; 5.Y.169.238; 5.Y.169.239; 5.Y.169.154; 5.Y.169.157; 5.Y.169.166; 5.Y.169.169; 5.Y.169.172; 5.Y.169.175; 5.Y.169.240; 5.Y.169.244; 5.Y.172.228; 5.Y.172.229; 5.Y.172.230; 5.Y.172.231; 5.Y.172.236; 5.Y.172.237; 5.Y.172.238; 5.Y.172.239; 5.Y.172.154; 5.Y.172.157; 5.Y.172.166; 5.Y.172.169; 5.Y.172.172; 5.Y.172.175; 5.Y.172.240; 5.Y.172.244; 5.Y.175.228; 5.Y.175.229; 5.Y.175.230; 5.Y.175.231; 5.Y.175.236; 5.Y.175.237; 5.Y.175.238; 5.Y.175.239; 5.Y.175.154; 5.Y.175.157; 5.Y.175.166; 5.Y.175.169; 5.Y.175.172; 5.Y.175.175; 5.Y.175.240; 5.Y.175.244; 5.Y.240.228; 5.Y.240.229; 5.Y.240.230; 5.Y.240.231; 5.Y.240.236; 5.Y.240.237; 5.Y.240.238; 5.Y.240.239; 5.Y.240.154; 5.Y.240.157; 5.Y.240.166; 5.Y.240.169; 5.Y.240.172; 5.Y.240.175; 5.Y.240.240; 5.Y.240.244; 5.Y.244.228; 5.Y.244.229; 5.Y.244.230; 5.Y.244.231; 5.Y.244.236; 5.Y.244.237;

5.Y.244.238; 5.Y.244.239; 5.Y.244.154; 5.Y.244.157; 5.Y.244.166; 5.Y.244.169; 5.Y.244.172; 5.Y.244.175; 5.Y.244.240; 5.Y.244.244;

Prodrugs of 6.B

6.B.228.228; 6.B.228.229; 6.B.228.230; 6.B.228.231; 6.B.228.236; 6.B.228.237; 6.B.228.238; 6.B.228.239; 6.B.228.154; 6.B.228.157; 6.B.228.166; 6.B.228.169; 6.B.228.172; 6.B.228.175; 6.B.228.240; 6.B.228.244; 6.B.229.228; 6.B.229.229; 6.B.229.230; 6.B.229.231; 6.B.229.236; 6.B.229.237; 6.B.229.238; 6.B.229.239; 6.B.229.154; 6.B.229.157; 6.B.229.166; 6.B.229.169; 6.B.229.172; 6.B.229.175; 6.B.229.240; 6.B.229.244; 6.B.230.228; 6.B.230.229; 6.B.230.230; 6.B.230.231; 6.B.230.236; 6.B.230.237; 6.B.230.238; 6.B.230.239; 6.B.230.154; 6.B.230.157; 6.B.230.166; 6.B.230.169; 6.B.230.172; 6.B.230.175; 6.B.230.240; 6.B.230.244; 6.B.231.228; 6.B.231.229; 6.B.231.230; 6.B.231.231; 6.B.231.236; 6.B.231.237; 6.B.231.238; 6.B.231.239; 6.B.231.154; 6.B.231.157; 6.B.231.166; 6.B.231.169; 6.B.231.172; 6.B.231.175; 6.B.231.240; 6.B.231.244; 6.B.236.228; 6.B.236.229; 6.B.236.230; 6.B.236.231; 6.B.236.236; 6.B.236.237; 6.B.236.238; 6.B.236.239; 6.B.236.154; 6.B.236.157; 6.B.236.166; 6.B.236.169; 6.B.236.172; 6.B.236.175; 6.B.236.240; 6.B.236.244; 6.B.237.228; 6.B.237.229; 6.B.237.230; 6.B.237.231; 6.B.237.236; 6.B.237.237; 6.B.237.238; 6.B.237.239; 6.B.237.154; 6.B.237.157; 6.B.237.166; 6.B.237.169; 6.B.237.172; 6.B.237.175; 6.B.237.240; 6.B.237.244; 6.B.238.228; 6.B.238.229; 6.B.238.230; 6.B.238.231; 6.B.238.236; 6.B.238.237; 6.B.238.238; 6.B.238.239; 6.B.238.154; 6.B.238.157; 6.B.238.166; 6.B.238.169; 6.B.238.172; 6.B.238.175; 6.B.238.240; 6.B.238.244; 6.B.239.228; 6.B.239.229; 6.B.239.230; 6.B.239.231; 6.B.239.236; 6.B.239.237; 6.B.239.238; 6.B.239.239; 6.B.239.154; 6.B.239.157; 6.B.239.166; 6.B.239.169; 6.B.239.172; 6.B.239.175; 6.B.239.240; 6.B.239.244; 6.B.154.228; 6.B.154.229; 6.B.154.230; 6.B.154.231; 6.B.154.236; 6.B.154.237; 6.B.154.238; 6.B.154.239; 6.B.154.154; 6.B.154.157; 6.B.154.166; 6.B.154.169; 6.B.154.172; 6.B.154.175; 6.B.154.240; 6.B.154.244; 6.B.157.228; 6.B.157.229; 6.B.157.230; 6.B.157.231; 6.B.157.236; 6.B.157.237; 6.B.157.238; 6.B.157.239; 6.B.157.154; 6.B.157.157; 6.B.157.166; 6.B.157.169; 6.B.157.172; 6.B.157.175; 6.B.157.240; 6.B.157.244; 6.B.166.228; 6.B.166.229; 6.B.166.230; 6.B.166.231; 6.B.166.236; 6.B.166.237; 6.B.166.238; 6.B.166.239; 6.B.166.154; 6.B.166.157; 6.B.166.166; 6.B.166.169; 6.B.166.172; 6.B.166.175; 6.B.166.240; 6.B.166.244; 6.B.169.228; 6.B.169.229; 6.B.169.230; 6.B.169.231; 6.B.169.236; 6.B.169.237; 6.B.169.238; 6.B.169.239; 6.B.169.154; 6.B.169.157; 6.B.169.166; 6.B.169.169; 6.B.169.172; 6.B.169.175; 6.B.169.240; 6.B.169.244; 6.B.172.228; 6.B.172.229; 6.B.172.230; 6.B.172.231; 6.B.172.236; 6.B.172.237; 6.B.172.238; 6.B.172.239; 6.B.172.154; 6.B.172.157; 6.B.172.166; 6.B.172.169; 6.B.172.172; 6.B.172.175; 6.B.172.240; 6.B.172.244; 6.B.175.228; 6.B.175.229; 6.B.175.230; 6.B.175.231; 6.B.175.236; 6.B.175.237; 6.B.175.238; 6.B.175.239; 6.B.175.154; 6.B.175.157; 6.B.175.166; 6.B.175.169; 6.B.175.172; 6.B.175.175; 6.B.175.240; 6.B.175.244; 6.B.240.228; 6.B.240.229; 6.B.240.230; 6.B.240.231; 6.B.240.236; 6.B.240.237; 6.B.240.238; 6.B.240.239; 6.B.240.154; 6.B.240.157; 6.B.240.166; 6.B.240.169; 6.B.240.172; 6.B.240.175; 6.B.240.240; 6.B.240.244; 6.B.244.228; 6.B.244.229; 6.B.244.230; 6.B.244.231; 6.B.244.236; 6.B.244.237; 6.B.244.238; 6.B.244.239; 6.B.244.154; 6.B.244.157; 6.B.244.166; 6.B.244.169; 6.B.244.172; 6.B.244.175; 6.B.244.240; 6.B.244.244;

Prodrugs of 6.D

6.D.228.228; 6.D.228.229; 6.D.228.230; 6.D.228.231; 6.D.228.236; 6.D.228.237; 6.D.228.238; 6.D.228.239; 6.D.228.154; 6.D.228.157; 6.D.228.166; 6.D.228.169; 6.D.228.172; 6.D.228.175; 6.D.228.240; 6.D.228.244; 6.D.229.228; 6.D.229.229;

6.D.229.230; 6.D.229.231; 6.D.229.236; 6.D.229.237; 6.D.229.238; 6.D.229.239; 6.D.229.154; 6.D.229.157; 6.D.229.166; 6.D.229.169; 6.D.229.172; 6.D.229.175; 6.D.229.240; 6.D.229.244; 6.D.230.228; 6.D.230.229; 6.D.230.230; 6.D.230.231; 6.D.230.236; 6.D.230.237; 6.D.230.238; 6.D.230.239; 6.D.230.154; 6.D.230.157; 6.D.230.166; 6.D.230.169; 6.D.230.172; 6.D.230.175; 6.D.230.240; 6.D.230.244; 6.D.231.228; 6.D.231.229; 6.D.231.230; 6.D.231.231; 6.D.231.236; 6.D.231.237; 6.D.231.238; 6.D.231.239; 6.D.231.154; 6.D.231.157; 6.D.231.166; 6.D.231.169; 6.D.231.172; 6.D.231.175; 6.D.231.240; 6.D.231.244; 6.D.236.228; 6.D.236.229; 6.D.236.230; 6.D.236.231; 6.D.236.236; 6.D.236.237; 6.D.236.238; 6.D.236.239; 6.D.236.154; 6.D.236.157; 6.D.236.166; 6.D.236.169; 6.D.236.172; 6.D.236.175; 6.D.236.240; 6.D.236.244; 6.D.237.228; 6.D.237.229; 6.D.237.230; 6.D.237.231; 6.D.237.236; 6.D.237.237; 6.D.237.238; 6.D.237.239; 6.D.237.154; 6.D.237.157; 6.D.237.166; 6.D.237.169; 6.D.237.172; 6.D.237.175; 6.D.237.240; 6.D.237.244; 6.D.238.228; 6.D.238.229; 6.D.238.230; 6.D.238.231; 6.D.238.236; 6.D.238.237; 6.D.238.238; 6.D.238.239; 6.D.238.154; 6.D.238.157; 6.D.238.166; 6.D.238.169; 6.D.238.172; 6.D.238.175; 6.D.238.240; 6.D.238.244; 6.D.239.228; 6.D.239.229; 6.D.239.230; 6.D.239.231; 6.D.239.236; 6.D.239.237; 6.D.239.238; 6.D.239.239; 6.D.239.154; 6.D.239.157; 6.D.239.166; 6.D.239.169; 6.D.239.172; 6.D.239.175; 6.D.239.240; 6.D.239.244; 6.D.154.228; 6.D.154.229; 6.D.154.230; 6.D.154.231; 6.D.154.236; 6.D.154.237; 6.D.154.238; 6.D.154.239; 6.D.154.154; 6.D.154.157; 6.D.154.166; 6.D.154.169; 6.D.154.172; 6.D.154.175; 6.D.154.240; 6.D.154.244; 6.D.157.228; 6.D.157.229; 6.D.157.230; 6.D.157.231; 6.D.157.236; 6.D.157.237; 6.D.157.238; 6.D.157.239; 6.D.157.154; 6.D.157.157; 6.D.157.166; 6.D.157.169; 6.D.157.172; 6.D.157.175; 6.D.157.240; 6.D.157.244; 6.D.166.228; 6.D.166.229; 6.D.166.230; 6.D.166.231; 6.D.166.236; 6.D.166.237; 6.D.166.238; 6.D.166.239; 6.D.166.154; 6.D.166.157; 6.D.166.166; 6.D.166.169; 6.D.166.172; 6.D.166.175; 6.D.166.240; 6.D.166.244; 6.D.169.228; 6.D.169.229; 6.D.169.230; 6.D.169.231; 6.D.169.236; 6.D.169.237; 6.D.169.238; 6.D.169.239; 6.D.169.154; 6.D.169.157; 6.D.169.166; 6.D.169.169; 6.D.169.172; 6.D.169.175; 6.D.169.240; 6.D.169.244; 6.D.172.228; 6.D.172.229; 6.D.172.230; 6.D.172.231; 6.D.172.236; 6.D.172.237; 6.D.172.238; 6.D.172.239; 6.D.172.154; 6.D.172.157; 6.D.172.166; 6.D.172.169; 6.D.172.172; 6.D.172.175; 6.D.172.240; 6.D.172.244; 6.D.175.228; 6.D.175.229; 6.D.175.230; 6.D.175.231; 6.D.175.236; 6.D.175.237; 6.D.175.238; 6.D.175.239; 6.D.175.154; 6.D.175.157; 6.D.175.166; 6.D.175.169; 6.D.175.172; 6.D.175.175; 6.D.175.240; 6.D.175.244; 6.D.240.228; 6.D.240.229; 6.D.240.230; 6.D.240.231; 6.D.240.236; 6.D.240.237; 6.D.240.238; 6.D.240.239; 6.D.240.154; 6.D.240.157; 6.D.240.166; 6.D.240.169; 6.D.240.172; 6.D.240.175; 6.D.240.240; 6.D.240.244; 6.D.244.228; 6.D.244.229; 6.D.244.230; 6.D.244.231; 6.D.244.236; 6.D.244.237; 6.D.244.238; 6.D.244.239; 6.D.244.154; 6.D.244.157; 6.D.244.166; 6.D.244.169; 6.D.244.172; 6.D.244.175; 6.D.244.240; 6.D.244.244;

Prodrugs of 6.E

6.E.228.228; 6.E.228.229; 6.E.228.230; 6.E.228.231; 6.E.228.236; 6.E.228.237; 6.E.228.238; 6.E.228.239; 6.E.228.154; 6.E.228.157; 6.E.228.166; 6.E.228.169; 6.E.228.172; 6.E.228.175; 6.E.228.240; 6.E.228.244; 6.E.229.228; 6.E.229.229; 6.E.229.230; 6.E.229.231; 6.E.229.236; 6.E.229.237; 6.E.229.238; 6.E.229.239; 6.E.229.154; 6.E.229.157; 6.E.229.166;

6.E.229.169; 6.E.229.172; 6.E.229.175; 6.E.229.240; 6.E.229.244; 6.E.230.228; 6.E.230.229; 6.E.230.230; 6.E.230.231; 6.E.230.236; 6.E.230.237; 6.E.230.238; 6.E.230.239; 6.E.230.154; 6.E.230.157; 6.E.230.166; 6.E.230.169; 6.E.230.172; 6.E.230.175; 6.E.230.240; 6.E.230.244; 6.E.231.228; 6.E.231.229; 6.E.231.230; 6.E.231.231; 6.E.231.236; 6.E.231.237; 6.E.231.238; 6.E.231.239; 6.E.231.154; 6.E.231.157; 6.E.231.166; 6.E.231.169; 6.E.231.172; 6.E.231.175; 6.E.231.240; 6.E.231.244; 6.E.236.228; 6.E.236.229; 6.E.236.230; 6.E.236.231; 6.E.236.236; 6.E.236.237; 6.E.236.238; 6.E.236.239; 6.E.236.154; 6.E.236.157; 6.E.236.166; 6.E.236.169; 6.E.236.172; 6.E.236.175; 6.E.236.240; 6.E.236.244; 6.E.237.228; 6.E.237.229; 6.E.237.230; 6.E.237.231; 6.E.237.236; 6.E.237.237; 6.E.237.238; 6.E.237.239; 6.E.237.154; 6.E.237.157; 6.E.237.166; 6.E.237.169; 6.E.237.172; 6.E.237.175; 6.E.237.240; 6.E.237.244; 6.E.238.228; 6.E.238.229; 6.E.238.230; 6.E.238.231; 6.E.238.236; 6.E.238.237; 6.E.238.238; 6.E.238.239; 6.E.238.154; 6.E.238.157; 6.E.238.166; 6.E.238.169; 6.E.238.172; 6.E.238.175; 6.E.238.240; 6.E.238.244; 6.E.239.228; 6.E.239.229; 6.E.239.230; 6.E.239.231; 6.E.239.236; 6.E.239.237; 6.E.239.238; 6.E.239.239; 6.E.239.154; 6.E.239.157; 6.E.239.166; 6.E.239.169; 6.E.239.172; 6.E.239.175; 6.E.239.240; 6.E.239.244; 6.E.154.228; 6.E.154.229; 6.E.154.230; 6.E.154.231; 6.E.154.236; 6.E.154.237; 6.E.154.238; 6.E.154.239; 6.E.154.154; 6.E.154.157; 6.E.154.166; 6.E.154.169; 6.E.154.172; 6.E.154.175; 6.E.154.240; 6.E.154.244; 6.E.157.228; 6.E.157.229; 6.E.157.230; 6.E.157.231; 6.E.157.236; 6.E.157.237; 6.E.157.238; 6.E.157.239; 6.E.157.154; 6.E.157.157; 6.E.157.166; 6.E.157.169; 6.E.157.172; 6.E.157.175; 6.E.157.240; 6.E.157.244; 6.E.166.228; 6.E.166.229; 6.E.166.230; 6.E.166.231; 6.E.166.236; 6.E.166.237; 6.E.166.238; 6.E.166.239; 6.E.166.154; 6.E.166.157; 6.E.166.166; 6.E.166.169; 6.E.166.172; 6.E.166.175; 6.E.166.240; 6.E.166.244; 6.E.169.228; 6.E.169.229; 6.E.169.230; 6.E.169.231; 6.E.169.236; 6.E.169.237; 6.E.169.238; 6.E.169.239; 6.E.169.154; 6.E.169.157; 6.E.169.166; 6.E.169.169; 6.E.169.172; 6.E.169.175; 6.E.169.240; 6.E.169.244; 6.E.172.228; 6.E.172.229; 6.E.172.230; 6.E.172.231; 6.E.172.236; 6.E.172.237; 6.E.172.238; 6.E.172.239; 6.E.172.154; 6.E.172.157; 6.E.172.166; 6.E.172.169; 6.E.172.172; 6.E.172.175; 6.E.172.240; 6.E.172.244; 6.E.175.228; 6.E.175.229; 6.E.175.230; 6.E.175.231; 6.E.175.236; 6.E.175.237; 6.E.175.238; 6.E.175.239; 6.E.175.154; 6.E.175.157; 6.E.175.166; 6.E.175.169; 6.E.175.172; 6.E.175.175; 6.E.175.240; 6.E.175.244; 6.E.240.228; 6.E.240.229; 6.E.240.230; 6.E.240.231; 6.E.240.236; 6.E.240.237; 6.E.240.238; 6.E.240.239; 6.E.240.154; 6.E.240.157; 6.E.240.166; 6.E.240.169; 6.E.240.172; 6.E.240.175; 6.E.240.240; 6.E.240.244; 6.E.244.228; 6.E.244.229; 6.E.244.230; 6.E.244.231; 6.E.244.236; 6.E.244.237; 6.E.244.238; 6.E.244.239; 6.E.244.154; 6.E.244.157; 6.E.244.166; 6.E.244.169; 6.E.244.172; 6.E.244.175; 6.E.244.240; 6.E.244.244;

<u>Prodrugs of 6.G</u>

6.G.228.228; 6.G.228.229; 6.G.228.230; 6.G.228.231; 6.G.228.236; 6.G.228.237; 6.G.228.238; 6.G.228.239; 6.G.228.154; 6.G.228.157; 6.G.228.166; 6.G.228.169; 6.G.228.172; 6.G.228.175; 6.G.228.240; 6.G.228.244; 6.G.229.228; 6.G.229.229; 6.G.229.230; 6.G.229.231; 6.G.229.236; 6.G.229.237; 6.G.229.238; 6.G.229.239; 6.G.229.154; 6.G.229.157; 6.G.229.166; 6.G.229.169; 6.G.229.172; 6.G.229.175; 6.G.229.240; 6.G.229.244; 6.G.230.228; 6.G.230.229; 6.G.230.230; 6.G.230.231; 6.G.230.236; 6.G.230.237; 6.G.230.238; 6.G.230.239; 6.G.230.154; 6.G.230.157; 6.G.230.166; 6.G.230.169; 6.G.230.172; 6.G.230.175; 6.G.230.240; 6.G.230.244; 6.G.231.228; 6.G.231.229; 6.G.231.230; 6.G.231.231; 6.G.231.236; 6.G.231.237; 6.G.231.238; 6.G.231.239; 6.G.231.154; 6.G.231.157; 6.G.231.166; 6.G.231.169; 6.G.231.172; 6.G.231.175; 6.G.231.240; 6.G.231.244; 6.G.236.228; 6.G.236.229;

6.G.236.230; 6.G.236.231; 6.G.236.236; 6.G.236.237; 6.G.236.238; 6.G.236.239; 6.G.236.154; 6.G.236.157; 6.G.236.166; 6.G.236.169; 6.G.236.172; 6.G.236.175; 6.G.236.240; 6.G.236.244; 6.G.237.228; 6.G.237.229; 6.G.237.230; 6.G.237.231; 6.G.237.236; 6.G.237.237; 6.G.237.238; 6.G.237.239; 6.G.237.154; 6.G.237.157; 6.G.237.166; 6.G.237.169; 6.G.237.172; 6.G.237.175; 6.G.237.240; 6.G.237.244; 6.G.238.228; 6.G.238.229; 6.G.238.230; 6.G.238.231; 6.G.238.236; 6.G.238.237; 6.G.238.238; 6.G.238.239; 6.G.238.154; 6.G.238.157; 6.G.238.166; 6.G.238.169; 6.G.238.172; 6.G.238.175; 6.G.238.240; 6.G.238.244; 6.G.239.228; 6.G.239.229; 6.G.239.230; 6.G.239.231; 6.G.239.236; 6.G.239.237; 6.G.239.238; 6.G.239.239; 6.G.239.154; 6.G.239.157; 6.G.239.166; 6.G.239.169; 6.G.239.172; 6.G.239.175; 6.G.239.240; 6.G.239.244; 6.G.154.228; 6.G.154.229; 6.G.154.230; 6.G.154.231; 6.G.154.236; 6.G.154.237; 6.G.154.238; 6.G.154.239; 6.G.154.154; 6.G.154.157; 6.G.154.166; 6.G.154.169; 6.G.154.172; 6.G.154.175; 6.G.154.240; 6.G.154.244; 6.G.157.228; 6.G.157.229; 6.G.157.230; 6.G.157.231; 6.G.157.236; 6.G.157.237; 6.G.157.238; 6.G.157.239; 6.G.157.154; 6.G.157.157; 6.G.157.166; 6.G.157.169; 6.G.157.172; 6.G.157.175; 6.G.157.240; 6.G.157.244; 6.G.166.228; 6.G.166.229; 6.G.166.230; 6.G.166.231; 6.G.166.236; 6.G.166.237; 6.G.166.238; 6.G.166.239; 6.G.166.154; 6.G.166.157; 6.G.166.166; 6.G.166.169; 6.G.166.172; 6.G.166.175; 6.G.166.240; 6.G.166.244; 6.G.169.228; 6.G.169.229; 6.G.169.230; 6.G.169.231; 6.G.169.236; 6.G.169.237; 6.G.169.238; 6.G.169.239; 6.G.169.154; 6.G.169.157; 6.G.169.166; 6.G.169.169; 6.G.169.172; 6.G.169.175; 6.G.169.240; 6.G.169.244; 6.G.172.228; 6.G.172.229; 6.G.172.230; 6.G.172.231; 6.G.172.236; 6.G.172.237; 6.G.172.238; 6.G.172.239; 6.G.172.154; 6.G.172.157; 6.G.172.166; 6.G.172.169; 6.G.172.172; 6.G.172.175; 6.G.172.240; 6.G.172.244; 6.G.175.228; 6.G.175.229; 6.G.175.230; 6.G.175.231; 6.G.175.236; 6.G.175.237; 6.G.175.238; 6.G.175.239; 6.G.175.154; 6.G.175.157; 6.G.175.166; 6.G.175.169; 6.G.175.172; 6.G.175.175; 6.G.175.240; 6.G.175.244; 6.G.240.228; 6.G.240.229; 6.G.240.230; 6.G.240.231; 6.G.240.236; 6.G.240.237; 6.G.240.238; 6.G.240.239; 6.G.240.154; 6.G.240.157; 6.G.240.166; 6.G.240.169; 6.G.240.172; 6.G.240.175; 6.G.240.240; 6.G.240.244; 6.G.244.228; 6.G.244.229; 6.G.244.230; 6.G.244.231; 6.G.244.236; 6.G.244.237; 6.G.244.238; 6.G.244.239; 6.G.244.154; 6.G.244.157; 6.G.244.166; 6.G.244.169; 6.G.244.172; 6.G.244.175; 6.G.244.240; 6.G.244.244;

Prodrugs of 6.I

6.I.228.228; 6.I.228.229; 6.I.228.230; 6.I.228.231; 6.I.228.236; 6.I.228.237; 6.I.228.238; 6.I.228.239; 6.I.228.154; 6.I.228.157; 6.I.228.166; 6.I.228.169; 6.I.228.172; 6.I.228.175; 6.I.228.240; 6.I.228.244; 6.I.229.228; 6.I.229.229; 6.I.229.230; 6.I.229.231; 6.I.229.236; 6.I.229.237; 6.I.229.238; 6.I.229.239; 6.I.229.154; 6.I.229.157; 6.I.229.166; 6.I.229.169; 6.I.229.172; 6.I.229.175; 6.I.229.240; 6.I.229.244; 6.I.230.228; 6.I.230.229; 6.I.230.230; 6.I.230.231; 6.I.230.236; 6.I.230.237; 6.I.230.238; 6.I.230.239; 6.I.230.154; 6.I.230.157; 6.I.230.166; 6.I.230.169; 6.I.230.172; 6.I.230.175; 6.I.230.240; 6.I.230.244; 6.I.231.228; 6.I.231.229; 6.I.231.230; 6.I.231.231; 6.I.231.236; 6.I.231.237; 6.I.231.238; 6.I.231.239; 6.I.231.154; 6.I.231.157; 6.I.231.166; 6.I.231.169; 6.I.231.172; 6.I.231.175; 6.I.231.240; 6.I.231.244; 6.I.236.228; 6.I.236.229; 6.I.236.230; 6.I.236.231; 6.I.236.236; 6.I.236.237; 6.I.236.238; 6.I.236.239; 6.I.236.154; 6.I.236.157; 6.I.236.166; 6.I.236.169; 6.I.236.172; 6.I.236.175; 6.I.236.240; 6.I.236.244; 6.I.237.228; 6.I.237.229; 6.I.237.230; 6.I.237.231;

6.I.237.236; 6.I.237.237; 6.I.237.238; 6.I.237.239; 6.I.237.154; 6.I.237.157; 6.I.237.166; 6.I.237.169; 6.I.237.172; 6.I.237.175; 6.I.237.240; 6.I.237.244; 6.I.238.228; 6.I.238.229; 6.I.238.230; 6.I.238.231; 6.I.238.236; 6.I.238.237; 6.I.238.238; 6.I.238.239; 6.I.238.154; 6.I.238.157; 6.I.238.166; 6.I.238.169; 6.I.238.172; 6.I.238.175; 6.I.238.240; 6.I.238.244; 6.I.239.228; 6.I.239.229; 6.I.239.230; 6.I.239.231; 6.I.239.236; 6.I.239.237; 6.I.239.238; 6.I.239.239; 6.I.239.154; 6.I.239.157; 6.I.239.166; 6.I.239.169; 6.I.239.172; 6.I.239.175; 6.I.239.240; 6.I.239.244; 6.I.154.228; 6.I.154.229; 6.I.154.230; 6.I.154.231; 6.I.154.236; 6.I.154.237; 6.I.154.238; 6.I.154.239; 6.I.154.154; 6.I.154.157; 6.I.154.166; 6.I.154.169; 6.I.154.172; 6.I.154.175; 6.I.154.240; 6.I.154.244; 6.I.157.228; 6.I.157.229; 6.I.157.230; 6.I.157.231; 6.I.157.236; 6.I.157.237; 6.I.157.238; 6.I.157.239; 6.I.157.154; 6.I.157.157; 6.I.157.166; 6.I.157.169; 6.I.157.172; 6.I.157.175; 6.I.157.240; 6.I.157.244; 6.I.166.228; 6.I.166.229; 6.I.166.230; 6.I.166.231; 6.I.166.236; 6.I.166.237; 6.I.166.238; 6.I.166.239; 6.I.166.154; 6.I.166.157; 6.I.166.166; 6.I.166.169; 6.I.166.172; 6.I.166.175; 6.I.166.240; 6.I.166.244; 6.I.169.228; 6.I.169.229; 6.I.169.230; 6.I.169.231; 6.I.169.236; 6.I.169.237; 6.I.169.238; 6.I.169.239; 6.I.169.154; 6.I.169.157; 6.I.169.166; 6.I.169.169; 6.I.169.172; 6.I.169.175; 6.I.169.240; 6.I.169.244; 6.I.172.228; 6.I.172.229; 6.I.172.230; 6.I.172.231; 6.I.172.236; 6.I.172.237; 6.I.172.238; 6.I.172.239; 6.I.172.154; 6.I.172.157; 6.I.172.166; 6.I.172.169; 6.I.172.172; 6.I.172.175; 6.I.172.240; 6.I.172.244; 6.I.175.228; 6.I.175.229; 6.I.175.230; 6.I.175.231; 6.I.175.236; 6.I.175.237; 6.I.175.238; 6.I.175.239; 6.I.175.154; 6.I.175.157; 6.I.175.166; 6.I.175.169; 6.I.175.172; 6.I.175.175; 6.I.175.240; 6.I.175.244; 6.I.240.228; 6.I.240.229; 6.I.240.230; 6.I.240.231; 6.I.240.236; 6.I.240.237; 6.I.240.238; 6.I.240.239; 6.I.240.154; 6.I.240.157; 6.I.240.166; 6.I.240.169; 6.I.240.172; 6.I.240.175; 6.I.240.240; 6.I.240.244; 6.I.244.228; 6.I.244.229; 6.I.244.230; 6.I.244.231; 6.I.244.236; 6.I.244.237; 6.I.244.238; 6.I.244.239; 6.I.244.154; 6.I.244.157; 6.I.244.166; 6.I.244.169; 6.I.244.172; 6.I.244.175; 6.I.244.240; 6.I.244.244;

Prodrugs of 6.J

6.J.228.228; 6.J.228.229; 6.J.228.230; 6.J.228.231; 6.J.228.236; 6.J.228.237; 6.J.228.238; 6.J.228.239; 6.J.228.154; 6.J.228.157; 6.J.228.166; 6.J.228.169; 6.J.228.172; 6.J.228.175; 6.J.228.240; 6.J.228.244; 6.J.229.228; 6.J.229.229; 6.J.229.230; 6.J.229.231; 6.J.229.236; 6.J.229.237; 6.J.229.238; 6.J.229.239; 6.J.229.154; 6.J.229.157; 6.J.229.166; 6.J.229.169; 6.J.229.172; 6.J.229.175; 6.J.229.240; 6.J.229.244; 6.J.230.228; 6.J.230.229; 6.J.230.230; 6.J.230.231; 6.J.230.236; 6.J.230.237; 6.J.230.238; 6.J.230.239; 6.J.230.154; 6.J.230.157; 6.J.230.166; 6.J.230.169; 6.J.230.172; 6.J.230.175; 6.J.230.240; 6.J.230.244; 6.J.231.228; 6.J.231.229; 6.J.231.230; 6.J.231.231; 6.J.231.236; 6.J.231.237; 6.J.231.238; 6.J.231.239; 6.J.231.154; 6.J.231.157; 6.J.231.166; 6.J.231.169; 6.J.231.172; 6.J.231.175; 6.J.231.240; 6.J.231.244; 6.J.236.228; 6.J.236.229; 6.J.236.230; 6.J.236.231; 6.J.236.236; 6.J.236.237; 6.J.236.238; 6.J.236.239; 6.J.236.154; 6.J.236.157; 6.J.236.166; 6.J.236.169; 6.J.236.172; 6.J.236.175; 6.J.236.240; 6.J.236.244; 6.J.237.228; 6.J.237.229; 6.J.237.230; 6.J.237.231; 6.J.237.236; 6.J.237.237; 6.J.237.238; 6.J.237.239; 6.J.237.154; 6.J.237.157; 6.J.237.166; 6.J.237.169; 6.J.237.172; 6.J.237.175; 6.J.237.240; 6.J.237.244; 6.J.238.228; 6.J.238.229; 6.J.238.230; 6.J.238.231; 6.J.238.236; 6.J.238.237; 6.J.238.238; 6.J.238.239; 6.J.238.154; 6.J.238.157; 6.J.238.166; 6.J.238.169; 6.J.238.172; 6.J.238.175; 6.J.238.240; 6.J.238.244; 6.J.239.228; 6.J.239.229; 6.J.239.230; 6.J.239.231; 6.J.239.236; 6.J.239.237; 6.J.239.238; 6.J.239.239; 6.J.239.154; 6.J.239.157; 6.J.239.166; 6.J.239.169; 6.J.239.172; 6.J.239.175; 6.J.239.240; 6.J.239.244; 6.J.154.228; 6.J.154.229; 6.J.154.230; 6.J.154.231; 6.J.154.236;

6.J.154.237; 6.J.154.238; 6.J.154.239; 6.J.154.154; 6.J.154.157; 6.J.154.166; 6.J.154.169; 6.J.154.172; 6.J.154.175; 6.J.154.240; 6.J.154.244; 6.J.157.228; 6.J.157.229; 6.J.157.230; 6.J.157.231; 6.J.157.236; 6.J.157.237; 6.J.157.238; 6.J.157.239; 6.J.157.154; 6.J.157.157; 6.J.157.166; 6.J.157.169; 6.J.157.172; 6.J.157.175; 6.J.157.240; 6.J.157.244; 6.J.166.228; 6.J.166.229; 6.J.166.230; 6.J.166.231; 6.J.166.236; 6.J.166.237; 6.J.166.238; 6.J.166.239; 6.J.166.154; 6.J.166.157; 6.J.166.166; 6.J.166.169; 6.J.166.172; 6.J.166.175; 6.J.166.240; 6.J.166.244; 6.J.169.228; 6.J.169.229; 6.J.169.230; 6.J.169.231; 6.J.169.236; 6.J.169.237; 6.J.169.238; 6.J.169.239; 6.J.169.154; 6.J.169.157; 6.J.169.166; 6.J.169.169; 6.J.169.172; 6.J.169.175; 6.J.169.240; 6.J.169.244; 6.J.172.228; 6.J.172.229; 6.J.172.230; 6.J.172.231; 6.J.172.236; 6.J.172.237; 6.J.172.238; 6.J.172.239; 6.J.172.154; 6.J.172.157; 6.J.172.166; 6.J.172.169; 6.J.172.172; 6.J.172.175; 6.J.172.240; 6.J.172.244; 6.J.175.228; 6.J.175.229; 6.J.175.230; 6.J.175.231; 6.J.175.236; 6.J.175.237; 6.J.175.238; 6.J.175.239; 6.J.175.154; 6.J.175.157; 6.J.175.166; 6.J.175.169; 6.J.175.172; 6.J.175.175; 6.J.175.240; 6.J.175.244; 6.J.240.228; 6.J.240.229; 6.J.240.230; 6.J.240.231; 6.J.240.236; 6.J.240.237; 6.J.240.238; 6.J.240.239; 6.J.240.154; 6.J.240.157; 6.J.240.166; 6.J.240.169; 6.J.240.172; 6.J.240.175; 6.J.240.240; 6.J.240.244; 6.J.244.228; 6.J.244.229; 6.J.244.230; 6.J.244.231; 6.J.244.236; 6.J.244.237; 6.J.244.238; 6.J.244.239; 6.J.244.154; 6.J.244.157; 6.J.244.166; 6.J.244.169; 6.J.244.172; 6.J.244.175; 6.J.244.240; 6.J.244.244;

Prodrugs of 6.L

6.L.228.228; 6.L.228.229; 6.L.228.230; 6.L.228.231; 6.L.228.236; 6.L.228.237; 6.L.228.238; 6.L.228.239; 6.L.228.154; 6.L.228.157; 6.L.228.166; 6.L.228.169; 6.L.228.172; 6.L.228.175; 6.L.228.240; 6.L.228.244; 6.L.229.228; 6.L.229.229; 6.L.229.230; 6.L.229.231; 6.L.229.236; 6.L.229.237; 6.L.229.238; 6.L.229.239; 6.L.229.154; 6.L.229.157; 6.L.229.166; 6.L.229.169; 6.L.229.172; 6.L.229.175; 6.L.229.240; 6.L.229.244; 6.L.230.228; 6.L.230.229; 6.L.230.230; 6.L.230.231; 6.L.230.236; 6.L.230.237; 6.L.230.238; 6.L.230.239; 6.L.230.154; 6.L.230.157; 6.L.230.166; 6.L.230.169; 6.L.230.172; 6.L.230.175; 6.L.230.240; 6.L.230.244; 6.L.231.228; 6.L.231.229; 6.L.231.230; 6.L.231.231; 6.L.231.236; 6.L.231.237; 6.L.231.238; 6.L.231.239; 6.L.231.154; 6.L.231.157; 6.L.231.166; 6.L.231.169; 6.L.231.172; 6.L.231.175; 6.L.231.240; 6.L.231.244; 6.L.236.228; 6.L.236.229; 6.L.236.230; 6.L.236.231; 6.L.236.236; 6.L.236.237; 6.L.236.238; 6.L.236.239; 6.L.236.154; 6.L.236.157; 6.L.236.166; 6.L.236.169; 6.L.236.172; 6.L.236.175; 6.L.236.240; 6.L.236.244; 6.L.237.228; 6.L.237.229; 6.L.237.230; 6.L.237.231; 6.L.237.236; 6.L.237.237; 6.L.237.238; 6.L.237.239; 6.L.237.154; 6.L.237.157; 6.L.237.166; 6.L.237.169; 6.L.237.172; 6.L.237.175; 6.L.237.240; 6.L.237.244; 6.L.238.228; 6.L.238.229; 6.L.238.230; 6.L.238.231; 6.L.238.236; 6.L.238.237; 6.L.238.238; 6.L.238.239; 6.L.238.154; 6.L.238.157; 6.L.238.166; 6.L.238.169; 6.L.238.172; 6.L.238.175; 6.L.238.240; 6.L.238.244; 6.L.239.228; 6.L.239.229; 6.L.239.230; 6.L.239.231; 6.L.239.236; 6.L.239.237; 6.L.239.238; 6.L.239.239; 6.L.239.154; 6.L.239.157; 6.L.239.166; 6.L.239.169; 6.L.239.172; 6.L.239.175; 6.L.239.240; 6.L.239.244; 6.L.154.228; 6.L.154.229; 6.L.154.230; 6.L.154.231; 6.L.154.236; 6.L.154.237; 6.L.154.238; 6.L.154.239; 6.L.154.154; 6.L.154.157; 6.L.154.166; 6.L.154.169; 6.L.154.172; 6.L.154.175; 6.L.154.240; 6.L.154.244; 6.L.157.228; 6.L.157.229; 6.L.157.230; 6.L.157.231; 6.L.157.236; 6.L.157.237; 6.L.157.238; 6.L.157.239; 6.L.157.154; 6.L.157.157; 6.L.157.166; 6.L.157.169; 6.L.157.172; 6.L.157.175; 6.L.157.240; 6.L.157.244; 6.L.166.228; 6.L.166.229; 6.L.166.230; 6.L.166.231; 6.L.166.236; 6.L.166.237; 6.L.166.238; 6.L.166.239; 6.L.166.154; 6.L.166.157; 6.L.166.166; 6.L.166.169; 6.L.166.172; 6.L.166.175; 6.L.166.240; 6.L.166.244; 6.L.169.228; 6.L.169.229; 6.L.169.230; 6.L.169.231; 6.L.169.236;

6.L.169.237; 6.L.169.238; 6.L.169.239; 6.L.169.154; 6.L.169.157; 6.L.169.166; 6.L.169.169; 6.L.169.172; 6.L.169.175; 6.L.169.240; 6.L.169.244; 6.L.172.228; 6.L.172.229; 6.L.172.230; 6.L.172.231; 6.L.172.236; 6.L.172.237; 6.L.172.238; 6.L.172.239; 6.L.172.154; 6.L.172.157; 6.L.172.166; 6.L.172.169; 6.L.172.172; 6.L.172.175; 6.L.172.240; 6.L.172.244; 6.L.175.228; 6.L.175.229; 6.L.175.230; 6.L.175.231; 6.L.175.236; 6.L.175.237; 6.L.175.238; 6.L.175.239; 6.L.175.154; 6.L.175.157; 6.L.175.166; 6.L.175.169; 6.L.175.172; 6.L.175.175; 6.L.175.240; 6.L.175.244; 6.L.240.228; 6.L.240.229; 6.L.240.230; 6.L.240.231; 6.L.240.236; 6.L.240.237; 6.L.240.238; 6.L.240.239; 6.L.240.154; 6.L.240.157; 6.L.240.166; 6.L.240.169; 6.L.240.172; 6.L.240.175; 6.L.240.240; 6.L.240.244; 6.L.244.228; 6.L.244.229; 6.L.244.230; 6.L.244.231; 6.L.244.236; 6.L.244.237; 6.L.244.238; 6.L.244.239; 6.L.244.154; 6.L.244.157; 6.L.244.166; 6.L.244.169; 6.L.244.172; 6.L.244.175; 6.L.244.240; 6.L.244.244;

Prodrugs of 6.O

6.O.228.228; 6.O.228.229; 6.O.228.230; 6.O.228.231; 6.O.228.236; 6.O.228.237; 6.O.228.238; 6.O.228.239; 6.O.228.154; 6.O.228.157; 6.O.228.166; 6.O.228.169; 6.O.228.172; 6.O.228.175; 6.O.228.240; 6.O.228.244; 6.O.229.228; 6.O.229.229; 6.O.229.230; 6.O.229.231; 6.O.229.236; 6.O.229.237; 6.O.229.238; 6.O.229.239; 6.O.229.154; 6.O.229.157; 6.O.229.166; 6.O.229.169; 6.O.229.172; 6.O.229.175; 6.O.229.240; 6.O.229.244; 6.O.230.228; 6.O.230.229; 6.O.230.230; 6.O.230.231; 6.O.230.236; 6.O.230.237; 6.O.230.238; 6.O.230.239; 6.O.230.154; 6.O.230.157; 6.O.230.166; 6.O.230.169; 6.O.230.172; 6.O.230.175; 6.O.230.240; 6.O.230.244; 6.O.231.228; 6.O.231.229; 6.O.231.230; 6.O.231.231; 6.O.231.236; 6.O.231.237; 6.O.231.238; 6.O.231.239; 6.O.231.154; 6.O.231.157; 6.O.231.166; 6.O.231.169; 6.O.231.172; 6.O.231.175; 6.O.231.240; 6.O.231.244; 6.O.236.228; 6.O.236.229; 6.O.236.230; 6.O.236.231; 6.O.236.236; 6.O.236.237; 6.O.236.238; 6.O.236.239; 6.O.236.154; 6.O.236.157; 6.O.236.166; 6.O.236.169; 6.O.236.172; 6.O.236.175; 6.O.236.240; 6.O.236.244; 6.O.237.228; 6.O.237.229; 6.O.237.230; 6.O.237.231; 6.O.237.236; 6.O.237.237; 6.O.237.238; 6.O.237.239; 6.O.237.154; 6.O.237.157; 6.O.237.166; 6.O.237.169; 6.O.237.172; 6.O.237.175; 6.O.237.240; 6.O.237.244; 6.O.238.228; 6.O.238.229; 6.O.238.230; 6.O.238.231; 6.O.238.236; 6.O.238.237; 6.O.238.238; 6.O.238.239; 6.O.238.154; 6.O.238.157; 6.O.238.166; 6.O.238.169; 6.O.238.172; 6.O.238.175; 6.O.238.240; 6.O.238.244; 6.O.239.228; 6.O.239.229; 6.O.239.230; 6.O.239.231; 6.O.239.236; 6.O.239.237; 6.O.239.238; 6.O.239.239; 6.O.239.154; 6.O.239.157; 6.O.239.166; 6.O.239.169; 6.O.239.172; 6.O.239.175; 6.O.239.240; 6.O.239.244; 6.O.154.228; 6.O.154.229; 6.O.154.230; 6.O.154.231; 6.O.154.236; 6.O.154.237; 6.O.154.238; 6.O.154.239; 6.O.154.154; 6.O.154.157; 6.O.154.166; 6.O.154.169; 6.O.154.172; 6.O.154.175; 6.O.154.240; 6.O.154.244; 6.O.157.228; 6.O.157.229; 6.O.157.230; 6.O.157.231; 6.O.157.236; 6.O.157.237; 6.O.157.238; 6.O.157.239; 6.O.157.154; 6.O.157.157; 6.O.157.166; 6.O.157.169; 6.O.157.172; 6.O.157.175; 6.O.157.240; 6.O.157.244; 6.O.166.228; 6.O.166.229; 6.O.166.230; 6.O.166.231; 6.O.166.236; 6.O.166.237; 6.O.166.238; 6.O.166.239; 6.O.166.154; 6.O.166.157; 6.O.166.166; 6.O.166.169; 6.O.166.172; 6.O.166.175; 6.O.166.240; 6.O.166.244; 6.O.169.228; 6.O.169.229; 6.O.169.230; 6.O.169.231; 6.O.169.236; 6.O.169.237; 6.O.169.238; 6.O.169.239; 6.O.169.154; 6.O.169.157; 6.O.169.166; 6.O.169.169; 6.O.169.172; 6.O.169.175; 6.O.169.240; 6.O.169.244; 6.O.172.228; 6.O.172.229; 6.O.172.230; 6.O.172.231; 6.O.172.236; 6.O.172.237;

6.O.172.238; 6.O.172.239; 6.O.172.154; 6.O.172.157; 6.O.172.166; 6.O.172.169; 6.O.172.172; 6.O.172.175; 6.O.172.240; 6.O.172.244; 6.O.175.228; 6.O.175.229; 6.O.175.230; 6.O.175.231; 6.O.175.236; 6.O.175.237; 6.O.175.238; 6.O.175.239; 6.O.175.154; 6.O.175.157; 6.O.175.166; 6.O.175.169; 6.O.175.172; 6.O.175.175; 6.O.175.240; 6.O.175.244; 6.O.240.228; 6.O.240.229; 6.O.240.230; 6.O.240.231; 6.O.240.236; 6.O.240.237; 6.O.240.238; 6.O.240.239; 6.O.240.154; 6.O.240.157; 6.O.240.166; 6.O.240.169; 6.O.240.172; 6.O.240.175; 6.O.240.240; 6.O.240.244; 6.O.244.228; 6.O.244.229; 6.O.244.230; 6.O.244.231; 6.O.244.236; 6.O.244.237; 6.O.244.238; 6.O.244.239; 6.O.244.154; 6.O.244.157; 6.O.244.166; 6.O.244.169; 6.O.244.172; 6.O.244.175; 6.O.244.240; 6.O.244.244;

Prodrugs of 6.P

6.P.228.228; 6.P.228.229; 6.P.228.230; 6.P.228.231; 6.P.228.236; 6.P.228.237; 6.P.228.238; 6.P.228.239; 6.P.228.154; 6.P.228.157; 6.P.228.166; 6.P.228.169; 6.P.228.172; 6.P.228.175; 6.P.228.240; 6.P.228.244; 6.P.229.228; 6.P.229.229; 6.P.229.230; 6.P.229.231; 6.P.229.236; 6.P.229.237; 6.P.229.238; 6.P.229.239; 6.P.229.154; 6.P.229.157; 6.P.229.166; 6.P.229.169; 6.P.229.172; 6.P.229.175; 6.P.229.240; 6.P.229.244; 6.P.230.228; 6.P.230.229; 6.P.230.230; 6.P.230.231; 6.P.230.236; 6.P.230.237; 6.P.230.238; 6.P.230.239; 6.P.230.154; 6.P.230.157; 6.P.230.166; 6.P.230.169; 6.P.230.172; 6.P.230.175; 6.P.230.240; 6.P.230.244; 6.P.231.228; 6.P.231.229; 6.P.231.230; 6.P.231.231; 6.P.231.236; 6.P.231.237; 6.P.231.238; 6.P.231.239; 6.P.231.154; 6.P.231.157; 6.P.231.166; 6.P.231.169; 6.P.231.172; 6.P.231.175; 6.P.231.240; 6.P.231.244; 6.P.236.228; 6.P.236.229; 6.P.236.230; 6.P.236.231; 6.P.236.236; 6.P.236.237; 6.P.236.238; 6.P.236.239; 6.P.236.154; 6.P.236.157; 6.P.236.166; 6.P.236.169; 6.P.236.172; 6.P.236.175; 6.P.236.240; 6.P.236.244; 6.P.237.228; 6.P.237.229; 6.P.237.230; 6.P.237.231; 6.P.237.236; 6.P.237.237; 6.P.237.238; 6.P.237.239; 6.P.237.154; 6.P.237.157; 6.P.237.166; 6.P.237.169; 6.P.237.172; 6.P.237.175; 6.P.237.240; 6.P.237.244; 6.P.238.228; 6.P.238.229; 6.P.238.230; 6.P.238.231; 6.P.238.236; 6.P.238.237; 6.P.238.238; 6.P.238.239; 6.P.238.154; 6.P.238.157; 6.P.238.166; 6.P.238.169; 6.P.238.172; 6.P.238.175; 6.P.238.240; 6.P.238.244; 6.P.239.228; 6.P.239.229; 6.P.239.230; 6.P.239.231; 6.P.239.236; 6.P.239.237; 6.P.239.238; 6.P.239.239; 6.P.239.154; 6.P.239.157; 6.P.239.166; 6.P.239.169; 6.P.239.172; 6.P.239.175; 6.P.239.240; 6.P.239.244; 6.P.154.228; 6.P.154.229; 6.P.154.230; 6.P.154.231; 6.P.154.236; 6.P.154.237; 6.P.154.238; 6.P.154.239; 6.P.154.154; 6.P.154.157; 6.P.154.166; 6.P.154.169; 6.P.154.172; 6.P.154.175; 6.P.154.240; 6.P.154.244; 6.P.157.228; 6.P.157.229; 6.P.157.230; 6.P.157.231; 6.P.157.236; 6.P.157.237; 6.P.157.238; 6.P.157.239; 6.P.157.154; 6.P.157.157; 6.P.157.166; 6.P.157.169; 6.P.157.172; 6.P.157.175; 6.P.157.240; 6.P.157.244; 6.P.166.228; 6.P.166.229; 6.P.166.230; 6.P.166.231; 6.P.166.236; 6.P.166.237; 6.P.166.238; 6.P.166.239; 6.P.166.154; 6.P.166.157; 6.P.166.166; 6.P.166.169; 6.P.166.172; 6.P.166.175; 6.P.166.240; 6.P.166.244; 6.P.169.228; 6.P.169.229; 6.P.169.230; 6.P.169.231; 6.P.169.236; 6.P.169.237; 6.P.169.238; 6.P.169.239; 6.P.169.154; 6.P.169.157; 6.P.169.166; 6.P.169.169; 6.P.169.172; 6.P.169.175; 6.P.169.240; 6.P.169.244; 6.P.172.228; 6.P.172.229; 6.P.172.230; 6.P.172.231; 6.P.172.236; 6.P.172.237; 6.P.172.238; 6.P.172.239; 6.P.172.154; 6.P.172.157; 6.P.172.166; 6.P.172.169; 6.P.172.172; 6.P.172.175; 6.P.172.240; 6.P.172.244; 6.P.175.228; 6.P.175.229; 6.P.175.230; 6.P.175.231; 6.P.175.236; 6.P.175.237; 6.P.175.238; 6.P.175.239; 6.P.175.154; 6.P.175.157; 6.P.175.166; 6.P.175.169; 6.P.175.172; 6.P.175.175; 6.P.175.240; 6.P.175.244; 6.P.240.228; 6.P.240.229; 6.P.240.230; 6.P.240.231; 6.P.240.236; 6.P.240.237; 6.P.240.238; 6.P.240.239; 6.P.240.154; 6.P.240.157; 6.P.240.166; 6.P.240.169; 6.P.240.172;

6.P.240.175; 6.P.240.240; 6.P.240.244; 6.P.244.228; 6.P.244.229; 6.P.244.230; 6.P.244.231; 6.P.244.236; 6.P.244.237; 6.P.244.238; 6.P.244.239; 6.P.244.154; 6.P.244.157; 6.P.244.166; 6.P.244.169; 6.P.244.172; 6.P.244.175; 6.P.244.240; 6.P.244.244;

Prodrugs of 6.U

6.U.228.228; 6.U.228.229; 6.U.228.230; 6.U.228.231; 6.U.228.236; 6.U.228.237; 6.U.228.238; 6.U.228.239; 6.U.228.154; 6.U.228.157; 6.U.228.166; 6.U.228.169; 6.U.228.172; 6.U.228.175; 6.U.228.240; 6.U.228.244; 6.U.229.228; 6.U.229.229; 6.U.229.230; 6.U.229.231; 6.U.229.236; 6.U.229.237; 6.U.229.238; 6.U.229.239; 6.U.229.154; 6.U.229.157; 6.U.229.166; 6.U.229.169; 6.U.229.172; 6.U.229.175; 6.U.229.240; 6.U.229.244; 6.U.230.228; 6.U.230.229; 6.U.230.230; 6.U.230.231; 6.U.230.236; 6.U.230.237; 6.U.230.238; 6.U.230.239; 6.U.230.154; 6.U.230.157; 6.U.230.166; 6.U.230.169; 6.U.230.172; 6.U.230.175; 6.U.230.240; 6.U.230.244; 6.U.231.228; 6.U.231.229; 6.U.231.230; 6.U.231.231; 6.U.231.236; 6.U.231.237; 6.U.231.238; 6.U.231.239; 6.U.231.154; 6.U.231.157; 6.U.231.166; 6.U.231.169; 6.U.231.172; 6.U.231.175; 6.U.231.240; 6.U.231.244; 6.U.236.228; 6.U.236.229; 6.U.236.230; 6.U.236.231; 6.U.236.236; 6.U.236.237; 6.U.236.238; 6.U.236.239; 6.U.236.154; 6.U.236.157; 6.U.236.166; 6.U.236.169; 6.U.236.172; 6.U.236.175; 6.U.236.240; 6.U.236.244; 6.U.237.228; 6.U.237.229; 6.U.237.230; 6.U.237.231; 6.U.237.236; 6.U.237.237; 6.U.237.238; 6.U.237.239; 6.U.237.154; 6.U.237.157; 6.U.237.166; 6.U.237.169; 6.U.237.172; 6.U.237.175; 6.U.237.240; 6.U.237.244; 6.U.238.228; 6.U.238.229; 6.U.238.230; 6.U.238.231; 6.U.238.236; 6.U.238.237; 6.U.238.238; 6.U.238.239; 6.U.238.154; 6.U.238.157; 6.U.238.166; 6.U.238.169; 6.U.238.172; 6.U.238.175; 6.U.238.240; 6.U.238.244; 6.U.239.228; 6.U.239.229; 6.U.239.230; 6.U.239.231; 6.U.239.236; 6.U.239.237; 6.U.239.238; 6.U.239.239; 6.U.239.154; 6.U.239.157; 6.U.239.166; 6.U.239.169; 6.U.239.172; 6.U.239.175; 6.U.239.240; 6.U.239.244; 6.U.154.228; 6.U.154.229; 6.U.154.230; 6.U.154.231; 6.U.154.236; 6.U.154.237; 6.U.154.238; 6.U.154.239; 6.U.154.154; 6.U.154.157; 6.U.154.166; 6.U.154.169; 6.U.154.172; 6.U.154.175; 6.U.154.240; 6.U.154.244; 6.U.157.228; 6.U.157.229; 6.U.157.230; 6.U.157.231; 6.U.157.236; 6.U.157.237; 6.U.157.238; 6.U.157.239; 6.U.157.154; 6.U.157.157; 6.U.157.166; 6.U.157.169; 6.U.157.172; 6.U.157.175; 6.U.157.240; 6.U.157.244; 6.U.166.228; 6.U.166.229; 6.U.166.230; 6.U.166.231; 6.U.166.236; 6.U.166.237; 6.U.166.238; 6.U.166.239; 6.U.166.154; 6.U.166.157; 6.U.166.166; 6.U.166.169; 6.U.166.172; 6.U.166.175; 6.U.166.240; 6.U.166.244; 6.U.169.228; 6.U.169.229; 6.U.169.230; 6.U.169.231; 6.U.169.236; 6.U.169.237; 6.U.169.238; 6.U.169.239; 6.U.169.154; 6.U.169.157; 6.U.169.166; 6.U.169.169; 6.U.169.172; 6.U.169.175; 6.U.169.240; 6.U.169.244; 6.U.172.228; 6.U.172.229; 6.U.172.230; 6.U.172.231; 6.U.172.236; 6.U.172.237; 6.U.172.238; 6.U.172.239; 6.U.172.154; 6.U.172.157; 6.U.172.166; 6.U.172.169; 6.U.172.172; 6.U.172.175; 6.U.172.240; 6.U.172.244; 6.U.175.228; 6.U.175.229; 6.U.175.230; 6.U.175.231; 6.U.175.236; 6.U.175.237; 6.U.175.238; 6.U.175.239; 6.U.175.154; 6.U.175.157; 6.U.175.166; 6.U.175.169; 6.U.175.172; 6.U.175.175; 6.U.175.240; 6.U.175.244; 6.U.240.228; 6.U.240.229; 6.U.240.230; 6.U.240.231; 6.U.240.236; 6.U.240.237; 6.U.240.238; 6.U.240.239; 6.U.240.154; 6.U.240.157; 6.U.240.166; 6.U.240.169; 6.U.240.172; 6.U.240.175; 6.U.240.240; 6.U.240.244; 6.U.244.228; 6.U.244.229; 6.U.244.230; 6.U.244.231; 6.U.244.236; 6.U.244.237;

6.U.244.238; 6.U.244.239; 6.U.244.154; 6.U.244.157; 6.U.244.166; 6.U.244.169; 6.U.244.172; 6.U.244.175; 6.U.244.240; 6.U.244.244;

Prodrugs of 6.W

6.W.228.228; 6.W.228.229; 6.W.228.230; 6.W.228.231; 6.W.228.236; 6.W.228.237; 6.W.228.238; 6.W.228.239; 6.W.228.154; 6.W.228.157; 6.W.228.166; 6.W.228.169; 6.W.228.172; 6.W.228.175; 6.W.228.240; 6.W.228.244; 6.W.229.228; 6.W.229.229; 6.W.229.230; 6.W.229.231; 6.W.229.236; 6.W.229.237; 6.W.229.238; 6.W.229.239; 6.W.229.154; 6.W.229.157; 6.W.229.166; 6.W.229.169; 6.W.229.172; 6.W.229.175; 6.W.229.240; 6.W.229.244; 6.W.230.228; 6.W.230.229; 6.W.230.230; 6.W.230.231; 6.W.230.236; 6.W.230.237; 6.W.230.238; 6.W.230.239; 6.W.230.154; 6.W.230.157; 6.W.230.166; 6.W.230.169; 6.W.230.172; 6.W.230.175; 6.W.230.240; 6.W.230.244; 6.W.231.228; 6.W.231.229; 6.W.231.230; 6.W.231.231; 6.W.231.236; 6.W.231.237; 6.W.231.238; 6.W.231.239; 6.W.231.154; 6.W.231.157; 6.W.231.166; 6.W.231.169; 6.W.231.172; 6.W.231.175; 6.W.231.240; 6.W.231.244; 6.W.236.228; 6.W.236.229; 6.W.236.230; 6.W.236.231; 6.W.236.236; 6.W.236.237; 6.W.236.238; 6.W.236.239; 6.W.236.154; 6.W.236.157; 6.W.236.166; 6.W.236.169; 6.W.236.172; 6.W.236.175; 6.W.236.240; 6.W.236.244; 6.W.237.228; 6.W.237.229; 6.W.237.230; 6.W.237.231; 6.W.237.236; 6.W.237.237; 6.W.237.238; 6.W.237.239; 6.W.237.154; 6.W.237.157; 6.W.237.166; 6.W.237.169; 6.W.237.172; 6.W.237.175; 6.W.237.240; 6.W.237.244; 6.W.238.228; 6.W.238.229; 6.W.238.230; 6.W.238.231; 6.W.238.236; 6.W.238.237; 6.W.238.238; 6.W.238.239; 6.W.238.154; 6.W.238.157; 6.W.238.166; 6.W.238.169; 6.W.238.172; 6.W.238.175; 6.W.238.240; 6.W.238.244; 6.W.239.228; 6.W.239.229; 6.W.239.230; 6.W.239.231; 6.W.239.236; 6.W.239.237; 6.W.239.238; 6.W.239.239; 6.W.239.154; 6.W.239.157; 6.W.239.166; 6.W.239.169; 6.W.239.172; 6.W.239.175; 6.W.239.240; 6.W.239.244; 6.W.154.228; 6.W.154.229; 6.W.154.230; 6.W.154.231; 6.W.154.236; 6.W.154.237; 6.W.154.238; 6.W.154.239; 6.W.154.154; 6.W.154.157; 6.W.154.166; 6.W.154.169; 6.W.154.172; 6.W.154.175; 6.W.154.240; 6.W.154.244; 6.W.157.228; 6.W.157.229; 6.W.157.230; 6.W.157.231; 6.W.157.236; 6.W.157.237; 6.W.157.238; 6.W.157.239; 6.W.157.154; 6.W.157.157; 6.W.157.166; 6.W.157.169; 6.W.157.172; 6.W.157.175; 6.W.157.240; 6.W.157.244; 6.W.166.228; 6.W.166.229; 6.W.166.230; 6.W.166.231; 6.W.166.236; 6.W.166.237; 6.W.166.238; 6.W.166.239; 6.W.166.154; 6.W.166.157; 6.W.166.166; 6.W.166.169; 6.W.166.172; 6.W.166.175; 6.W.166.240; 6.W.166.244; 6.W.169.228; 6.W.169.229; 6.W.169.230; 6.W.169.231; 6.W.169.236; 6.W.169.237; 6.W.169.238; 6.W.169.239; 6.W.169.154; 6.W.169.157; 6.W.169.166; 6.W.169.169; 6.W.169.172; 6.W.169.175; 6.W.169.240; 6.W.169.244; 6.W.172.228; 6.W.172.229; 6.W.172.230; 6.W.172.231; 6.W.172.236; 6.W.172.237; 6.W.172.238; 6.W.172.239; 6.W.172.154; 6.W.172.157; 6.W.172.166; 6.W.172.169; 6.W.172.172; 6.W.172.175; 6.W.172.240; 6.W.172.244; 6.W.175.228; 6.W.175.229; 6.W.175.230; 6.W.175.231; 6.W.175.236; 6.W.175.237; 6.W.175.238; 6.W.175.239; 6.W.175.154; 6.W.175.157; 6.W.175.166; 6.W.175.169; 6.W.175.172; 6.W.175.175; 6.W.175.240; 6.W.175.244; 6.W.240.228; 6.W.240.229; 6.W.240.230; 6.W.240.231; 6.W.240.236; 6.W.240.237; 6.W.240.238; 6.W.240.239; 6.W.240.154; 6.W.240.157; 6.W.240.166; 6.W.240.169; 6.W.240.172; 6.W.240.175; 6.W.240.240; 6.W.240.244; 6.W.244.228; 6.W.244.229; 6.W.244.230; 6.W.244.231; 6.W.244.236; 6.W.244.237;

6.W.244.238; 6.W.244.239; 6.W.244.154; 6.W.244.157; 6.W.244.166; 6.W.244.169; 6.W.244.172; 6.W.244.175; 6.W.244.240; 6.W.244.244;

Prodrugs of 6.Y

6.Y.228.228; 6.Y.228.229; 6.Y.228.230; 6.Y.228.231; 6.Y.228.236; 6.Y.228.237; 6.Y.228.238; 6.Y.228.239; 6.Y.228.154; 6.Y.228.157; 6.Y.228.166; 6.Y.228.169; 6.Y.228.172; 6.Y.228.175; 6.Y.228.240; 6.Y.228.244; 6.Y.229.228; 6.Y.229.229; 6.Y.229.230; 6.Y.229.231; 6.Y.229.236; 6.Y.229.237; 6.Y.229.238; 6.Y.229.239; 6.Y.229.154; 6.Y.229.157; 6.Y.229.166; 6.Y.229.169; 6.Y.229.172; 6.Y.229.175; 6.Y.229.240; 6.Y.229.244; 6.Y.230.228; 6.Y.230.229; 6.Y.230.230; 6.Y.230.231; 6.Y.230.236; 6.Y.230.237; 6.Y.230.238; 6.Y.230.239; 6.Y.230.154; 6.Y.230.157; 6.Y.230.166; 6.Y.230.169; 6.Y.230.172; 6.Y.230.175; 6.Y.230.240; 6.Y.230.244; 6.Y.231.228; 6.Y.231.229; 6.Y.231.230; 6.Y.231.231; 6.Y.231.236; 6.Y.231.237; 6.Y.231.238; 6.Y.231.239; 6.Y.231.154; 6.Y.231.157; 6.Y.231.166; 6.Y.231.169; 6.Y.231.172; 6.Y.231.175; 6.Y.231.240; 6.Y.231.244; 6.Y.236.228; 6.Y.236.229; 6.Y.236.230; 6.Y.236.231; 6.Y.236.236; 6.Y.236.237; 6.Y.236.238; 6.Y.236.239; 6.Y.236.154; 6.Y.236.157; 6.Y.236.166; 6.Y.236.169; 6.Y.236.172; 6.Y.236.175; 6.Y.236.240; 6.Y.236.244; 6.Y.237.228; 6.Y.237.229; 6.Y.237.230; 6.Y.237.231; 6.Y.237.236; 6.Y.237.237; 6.Y.237.238; 6.Y.237.239; 6.Y.237.154; 6.Y.237.157; 6.Y.237.166; 6.Y.237.169; 6.Y.237.172; 6.Y.237.175; 6.Y.237.240; 6.Y.237.244; 6.Y.238.228; 6.Y.238.229; 6.Y.238.230; 6.Y.238.231; 6.Y.238.236; 6.Y.238.237; 6.Y.238.238; 6.Y.238.239; 6.Y.238.154; 6.Y.238.157; 6.Y.238.166; 6.Y.238.169; 6.Y.238.172; 6.Y.238.175; 6.Y.238.240; 6.Y.238.244; 6.Y.239.228; 6.Y.239.229; 6.Y.239.230; 6.Y.239.231; 6.Y.239.236; 6.Y.239.237; 6.Y.239.238; 6.Y.239.239; 6.Y.239.154; 6.Y.239.157; 6.Y.239.166; 6.Y.239.169; 6.Y.239.172; 6.Y.239.175; 6.Y.239.240; 6.Y.239.244; 6.Y.154.228; 6.Y.154.229; 6.Y.154.230; 6.Y.154.231; 6.Y.154.236; 6.Y.154.237; 6.Y.154.238; 6.Y.154.239; 6.Y.154.154; 6.Y.154.157; 6.Y.154.166; 6.Y.154.169; 6.Y.154.172; 6.Y.154.175; 6.Y.154.240; 6.Y.154.244; 6.Y.157.228; 6.Y.157.229; 6.Y.157.230; 6.Y.157.231; 6.Y.157.236; 6.Y.157.237; 6.Y.157.238; 6.Y.157.239; 6.Y.157.154; 6.Y.157.157; 6.Y.157.166; 6.Y.157.169; 6.Y.157.172; 6.Y.157.175; 6.Y.157.240; 6.Y.157.244; 6.Y.166.228; 6.Y.166.229; 6.Y.166.230; 6.Y.166.231; 6.Y.166.236; 6.Y.166.237; 6.Y.166.238; 6.Y.166.239; 6.Y.166.154; 6.Y.166.157; 6.Y.166.166; 6.Y.166.169; 6.Y.166.172; 6.Y.166.175; 6.Y.166.240; 6.Y.166.244; 6.Y.169.228; 6.Y.169.229; 6.Y.169.230; 6.Y.169.231; 6.Y.169.236; 6.Y.169.237; 6.Y.169.238; 6.Y.169.239; 6.Y.169.154; 6.Y.169.157; 6.Y.169.166; 6.Y.169.169; 6.Y.169.172; 6.Y.169.175; 6.Y.169.240; 6.Y.169.244; 6.Y.172.228; 6.Y.172.229; 6.Y.172.230; 6.Y.172.231; 6.Y.172.236; 6.Y.172.237; 6.Y.172.238; 6.Y.172.239; 6.Y.172.154; 6.Y.172.157; 6.Y.172.166; 6.Y.172.169; 6.Y.172.172; 6.Y.172.175; 6.Y.172.240; 6.Y.172.244; 6.Y.175.228; 6.Y.175.229; 6.Y.175.230; 6.Y.175.231; 6.Y.175.236; 6.Y.175.237; 6.Y.175.238; 6.Y.175.239; 6.Y.175.154; 6.Y.175.157; 6.Y.175.166; 6.Y.175.169; 6.Y.175.172; 6.Y.175.175; 6.Y.175.240; 6.Y.175.244; 6.Y.240.228; 6.Y.240.229; 6.Y.240.230; 6.Y.240.231; 6.Y.240.236; 6.Y.240.237; 6.Y.240.238; 6.Y.240.239; 6.Y.240.154; 6.Y.240.157; 6.Y.240.166; 6.Y.240.169; 6.Y.240.172; 6.Y.240.175; 6.Y.240.240; 6.Y.240.244; 6.Y.244.228; 6.Y.244.229; 6.Y.244.230; 6.Y.244.231; 6.Y.244.236; 6.Y.244.237; 6.Y.244.238; 6.Y.244.239; 6.Y.244.154; 6.Y.244.157; 6.Y.244.166; 6.Y.244.169; 6.Y.244.172; 6.Y.244.175; 6.Y.244.240; 6.Y.244.244;

Prodrugs of 7.AH

7.AH.4.157; 7.AH.4.158; 7.AH.4.196; 7.AH.4.223; 7.AH.4.240; 7.AH.4.244; 7.AH.4.243; 7.AH.4.247; 7.AH.5.157; 7.AH.5.158; 7.AH.5.196; 7.AH.5.223; 7.AH.5.240; 7.AH.5.244; 7.AH.5.243; 7.AH.5.247; 7.AH.7.157; 7.AH.7.158; 7.AH.7.196; 7.AH.7.223; 7.AH.7.240; 7.AH.7.244; 7.AH.7.243; 7.AH.7.247; 7.AH.15.157; 7.AH.15.158; 7.AH.15.196; 7.AH.15.223; 7.AH.15.240; 7.AH.15.244; 7.AH.15.243; 7.AH.15.247; 7.AH.16.157; 7.AH.16.158; 7.AH.16.196; 7.AH.16.223; 7.AH.16.240; 7.AH.16.244; 7.AH.16.243; 7.AH.16.247; 7.AH.18.157; 7.AH.18.158; 7.AH.18.196; 7.AH.18.223; 7.AH.18.240; 7.AH.18.244; 7.AH.18.243; 7.AH.18.247; 7.AH.26.157; 7.AH.26.158; 7.AH.26.196; 7.AH.26.223; 7.AH.26.240; 7.AH.26.244; 7.AH.26.243; 7.AH.26.247; 7.AH.27.157; 7.AH.27.158; 7.AH.27.196; 7.AH.27.223; 7.AH.27.240; 7.AH.27.244; 7.AH.27.243; 7.AH.27.247; 7.AH.29.157; 7.AH.29.158; 7.AH.29.196; 7.AH.29.223; 7.AH.29.240; 7.AH.29.244; 7.AH.29.243; 7.AH.29.247; 7.AH.54.157; 7.AH.54.158; 7.AH.54.196; 7.AH.54.223; 7.AH.54.240; 7.AH.54.244; 7.AH.54.243; 7.AH.54.247; 7.AH.55.157; 7.AH.55.158; 7.AH.55.196; 7.AH.55.223; 7.AH.55.240; 7.AH.55.244; 7.AH.55.243; 7.AH.55.247; 7.AH.56.157; 7.AH.56.158; 7.AH.56.196; 7.AH.56.223; 7.AH.56.240; 7.AH.56.244; 7.AH.56.243; 7.AH.56.247; 7.AH.157.157; 7.AH.157.158; 7.AH.157.196; 7.AH.157.223; 7.AH.157.240; 7.AH.157.244; 7.AH.157.243; 7.AH.157.247; 7.AH.196.157; 7.AH.196.158; 7.AH.196.196; 7.AH.196.223; 7.AH.196.240; 7.AH.196.244; 7.AH.196.243; 7.AH.196.247; 7.AH.223.157; 7.AH.223.158; 7.AH.223.196; 7.AH.223.223; 7.AH.223.240; 7.AH.223.244; 7.AH.223.243; 7.AH.223.247; 7.AH.240.157; 7.AH.240.158; 7.AH.240.196; 7.AH.240.223; 7.AH.240.240; 7.AH.240.244; 7.AH.240.243; 7.AH.240.247; 7.AH.244.157; 7.AH.244.158; 7.AH.244.196; 7.AH.244.223; 7.AH.244.240; 7.AH.244.244; 7.AH.244.243; 7.AH.244.247; 7.AH.247.157; 7.AH.247.158; 7.AH.247.196; 7.AH.247.223; 7.AH.247.240; 7.AH.247.244; 7.AH.247.243; 7.AH.247.247;

Prodrugs of 7.AJ

7.AJ.4.157; 7.AJ.4.158; 7.AJ.4.196; 7.AJ.4.223; 7.AJ.4.240; 7.AJ.4.244; 7.AJ.4.243; 7.AJ.4.247; 7.AJ.5.157; 7.AJ.5.158; 7.AJ.5.196; 7.AJ.5.223; 7.AJ.5.240; 7.AJ.5.244; 7.AJ.5.243; 7.AJ.5.247; 7.AJ.7.157; 7.AJ.7.158; 7.AJ.7.196; 7.AJ.7.223; 7.AJ.7.240; 7.AJ.7.244; 7.AJ.7.243; 7.AJ.7.247; 7.AJ.15.157; 7.AJ.15.158; 7.AJ.15.196; 7.AJ.15.223; 7.AJ.15.240; 7.AJ.15.244; 7.AJ.15.243; 7.AJ.15.247; 7.AJ.16.157; 7.AJ.16.158; 7.AJ.16.196; 7.AJ.16.223; 7.AJ.16.240; 7.AJ.16.244; 7.AJ.16.243; 7.AJ.16.247; 7.AJ.18.157; 7.AJ.18.158; 7.AJ.18.196; 7.AJ.18.223; 7.AJ.18.240; 7.AJ.18.244; 7.AJ.18.243; 7.AJ.18.247; 7.AJ.26.157; 7.AJ.26.158; 7.AJ.26.196; 7.AJ.26.223; 7.AJ.26.240; 7.AJ.26.244; 7.AJ.26.243; 7.AJ.26.247; 7.AJ.27.157; 7.AJ.27.158; 7.AJ.27.196; 7.AJ.27.223; 7.AJ.27.240; 7.AJ.27.244; 7.AJ.27.243; 7.AJ.27.247; 7.AJ.29.157; 7.AJ.29.158; 7.AJ.29.196; 7.AJ.29.223; 7.AJ.29.240; 7.AJ.29.244; 7.AJ.29.243; 7.AJ.29.247; 7.AJ.54.157; 7.AJ.54.158; 7.AJ.54.196; 7.AJ.54.223; 7.AJ.54.240; 7.AJ.54.244; 7.AJ.54.243; 7.AJ.54.247; 7.AJ.55.157; 7.AJ.55.158; 7.AJ.55.196; 7.AJ.55.223; 7.AJ.55.240; 7.AJ.55.244; 7.AJ.55.243; 7.AJ.55.247; 7.AJ.56.157; 7.AJ.56.158; 7.AJ.56.196; 7.AJ.56.223; 7.AJ.56.240; 7.AJ.56.244; 7.AJ.56.243; 7.AJ.56.247; 7.AJ.157.157; 7.AJ.157.158; 7.AJ.157.196; 7.AJ.157.223; 7.AJ.157.240; 7.AJ.157.244; 7.AJ.157.243; 7.AJ.157.247; 7.AJ.196.157; 7.AJ.196.158; 7.AJ.196.196; 7.AJ.196.223; 7.AJ.196.240; 7.AJ.196.244; 7.AJ.196.243; 7.AJ.196.247; 7.AJ.223.157; 7.AJ.223.158; 7.AJ.223.196; 7.AJ.223.223; 7.AJ.223.240; 7.AJ.223.244; 7.AJ.223.243; 7.AJ.223.247; 7.AJ.240.157; 7.AJ.240.158; 7.AJ.240.196; 7.AJ.240.223; 7.AJ.240.240; 7.AJ.240.244; 7.AJ.240.243; 7.AJ.240.247; 7.AJ.244.157; 7.AJ.244.158; 7.AJ.244.196; 7.AJ.244.223; 7.AJ.244.240;

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Prodrugs of 7.AN

7.AN.4.157; 7.AN.4.158; 7.AN.4.196; 7.AN.4.223; 7.AN.4.240; 7.AN.4.244; 7.AN.4.243; 7.AN.4.247; 7.AN.5.157; 7.AN.5.158; 7.AN.5.196; 7.AN.5.223; 7.AN.5.240; 7.AN.5.244; 7.AN.5.243; 7.AN.5.247; 7.AN.7.157; 7.AN.7.158; 7.AN.7.196; 7.AN.7.223; 7.AN.7.240; 7.AN.7.244; 7.AN.7.243; 7.AN.7.247; 7.AN.15.157; 7.AN.15.158; 7.AN.15.196; 7.AN.15.223; 7.AN.15.240; 7.AN.15.244; 7.AN.15.243; 7.AN.15.247; 7.AN.16.157; 7.AN.16.158; 7.AN.16.196; 7.AN.16.223; 7.AN.16.240; 7.AN.16.244; 7.AN.16.243; 7.AN.16.247; 7.AN.18.157; 7.AN.18.158; 7.AN.18.196; 7.AN.18.223; 7.AN.18.240; 7.AN.18.244; 7.AN.18.243; 7.AN.18.247; 7.AN.26.157; 7.AN.26.158; 7.AN.26.196; 7.AN.26.223; 7.AN.26.240; 7.AN.26.244; 7.AN.26.243; 7.AN.26.247; 7.AN.27.157; 7.AN.27.158; 7.AN.27.196; 7.AN.27.223; 7.AN.27.240; 7.AN.27.244; 7.AN.27.243; 7.AN.27.247; 7.AN.29.157; 7.AN.29.158; 7.AN.29.196; 7.AN.29.223; 7.AN.29.240; 7.AN.29.244; 7.AN.29.243; 7.AN.29.247; 7.AN.54.157; 7.AN.54.158; 7.AN.54.196; 7.AN.54.223; 7.AN.54.240; 7.AN.54.244; 7.AN.54.243; 7.AN.54.247; 7.AN.55.157; 7.AN.55.158; 7.AN.55.196; 7.AN.55.223; 7.AN.55.240; 7.AN.55.244; 7.AN.55.243; 7.AN.55.247; 7.AN.56.157; 7.AN.56.158; 7.AN.56.196; 7.AN.56.223; 7.AN.56.240; 7.AN.56.244; 7.AN.56.243; 7.AN.56.247; 7.AN.157.157; 7.AN.157.158; 7.AN.157.196; 7.AN.157.223; 7.AN.157.240; 7.AN.157.244; 7.AN.157.243; 7.AN.157.247; 7.AN.196.157; 7.AN.196.158; 7.AN.196.196; 7.AN.196.223; 7.AN.196.240; 7.AN.196.244; 7.AN.196.243; 7.AN.196.247; 7.AN.223.157; 7.AN.223.158; 7.AN.223.196; 7.AN.223.223; 7.AN.223.240; 7.AN.223.244; 7.AN.223.243; 7.AN.223.247; 7.AN.240.157; 7.AN.240.158; 7.AN.240.196; 7.AN.240.223; 7.AN.240.240; 7.AN.240.244; 7.AN.240.243; 7.AN.240.247; 7.AN.244.157; 7.AN.244.158; 7.AN.244.196; 7.AN.244.223; 7.AN.244.240; 7.AN.244.244; 7.AN.244.243; 7.AN.244.247; 7.AN.247.157; 7.AN.247.158; 7.AN.247.196; 7.AN.247.223; 7.AN.247.240; 7.AN.247.244; 7.AN.247.243; 7.AN.247.247;

Prodrugs of 7.AP

7.AP.4.157; 7.AP.4.158; 7.AP.4.196; 7.AP.4.223; 7.AP.4.240; 7.AP.4.244; 7.AP.4.243; 7.AP.4.247; 7.AP.5.157; 7.AP.5.158; 7.AP.5.196; 7.AP.5.223; 7.AP.5.240; 7.AP.5.244; 7.AP.5.243; 7.AP.5.247; 7.AP.7.157; 7.AP.7.158; 7.AP.7.196; 7.AP.7.223; 7.AP.7.240; 7.AP.7.244; 7.AP.7.243; 7.AP.7.247; 7.AP.15.157; 7.AP.15.158; 7.AP.15.196; 7.AP.15.223; 7.AP.15.240; 7.AP.15.244; 7.AP.15.243; 7.AP.15.247; 7.AP.16.157; 7.AP.16.158; 7.AP.16.196; 7.AP.16.223; 7.AP.16.240; 7.AP.16.244; 7.AP.16.243; 7.AP.16.247; 7.AP.18.157; 7.AP.18.158; 7.AP.18.196; 7.AP.18.223; 7.AP.18.240; 7.AP.18.244; 7.AP.18.243; 7.AP.18.247; 7.AP.26.157; 7.AP.26.158; 7.AP.26.196; 7.AP.26.223; 7.AP.26.240; 7.AP.26.244; 7.AP.26.243; 7.AP.26.247; 7.AP.27.157; 7.AP.27.158; 7.AP.27.196; 7.AP.27.223; 7.AP.27.240; 7.AP.27.244; 7.AP.27.243; 7.AP.27.247; 7.AP.29.157; 7.AP.29.158; 7.AP.29.196; 7.AP.29.223; 7.AP.29.240; 7.AP.29.244; 7.AP.29.243; 7.AP.29.247; 7.AP.54.157; 7.AP.54.158; 7.AP.54.196; 7.AP.54.223; 7.AP.54.240; 7.AP.54.244; 7.AP.54.243; 7.AP.54.247; 7.AP.55.157; 7.AP.55.158; 7.AP.55.196; 7.AP.55.223; 7.AP.55.240; 7.AP.55.244; 7.AP.55.243; 7.AP.55.247; 7.AP.56.157; 7.AP.56.158; 7.AP.56.196; 7.AP.56.223; 7.AP.56.240; 7.AP.56.244; 7.AP.56.243; 7.AP.56.247; 7.AP.157.157; 7.AP.157.158; 7.AP.157.196; 7.AP.157.223; 7.AP.157.240; 7.AP.157.244; 7.AP.157.243; 7.AP.157.247; 7.AP.196.157; 7.AP.196.158; 7.AP.196.196; 7.AP.196.223; 7.AP.196.240; 7.AP.196.244; 7.AP.196.243; 7.AP.196.247;

7.AP.223.157; 7.AP.223.158; 7.AP.223.196; 7.AP.223.223; 7.AP.223.240; 7.AP.223.244; 7.AP.223.243; 7.AP.223.247; 7.AP.240.157; 7.AP.240.158; 7.AP.240.196; 7.AP.240.223; 7.AP.240.240; 7.AP.240.244; 7.AP.240.243; 7.AP.240.247; 7.AP.244.157; 7.AP.244.158; 7.AP.244.196; 7.AP.244.223; 7.AP.244.240; 7.AP.244.244; 7.AP.244.243; 7.AP.244.247; 7.AP.247.157; 7.AP.247.158; 7.AP.247.196; 7.AP.247.223; 7.AP.247.240; 7.AP.247.244; 7.AP.247.243; 7.AP.247.247;

Prodrugs of 7.AZ

7.AZ.4.157; 7.AZ.4.158; 7.AZ.4.196; 7.AZ.4.223; 7.AZ.4.240; 7.AZ.4.244; 7.AZ.4.243; 7.AZ.4.247; 7.AZ.5.157; 7.AZ.5.158; 7.AZ.5.196; 7.AZ.5.223; 7.AZ.5.240; 7.AZ.5.244; 7.AZ.5.243; 7.AZ.5.247; 7.AZ.7.157; 7.AZ.7.158; 7.AZ.7.196; 7.AZ.7.223; 7.AZ.7.240; 7.AZ.7.244; 7.AZ.7.243; 7.AZ.7.247; 7.AZ.15.157; 7.AZ.15.158; 7.AZ.15.196; 7.AZ.15.223; 7.AZ.15.240; 7.AZ.15.244; 7.AZ.15.243; 7.AZ.15.247; 7.AZ.16.157; 7.AZ.16.158; 7.AZ.16.196; 7.AZ.16.223; 7.AZ.16.240; 7.AZ.16.244; 7.AZ.16.243; 7.AZ.16.247; 7.AZ.18.157; 7.AZ.18.158; 7.AZ.18.196; 7.AZ.18.223; 7.AZ.18.240; 7.AZ.18.244; 7.AZ.18.243; 7.AZ.18.247; 7.AZ.26.157; 7.AZ.26.158; 7.AZ.26.196; 7.AZ.26.223; 7.AZ.26.240; 7.AZ.26.244; 7.AZ.26.243; 7.AZ.26.247; 7.AZ.27.157; 7.AZ.27.158; 7.AZ.27.196; 7.AZ.27.223; 7.AZ.27.240; 7.AZ.27.244; 7.AZ.27.243; 7.AZ.27.247; 7.AZ.29.157; 7.AZ.29.158; 7.AZ.29.196; 7.AZ.29.223; 7.AZ.29.240; 7.AZ.29.244; 7.AZ.29.243; 7.AZ.29.247; 7.AZ.54.157; 7.AZ.54.158; 7.AZ.54.196; 7.AZ.54.223; 7.AZ.54.240; 7.AZ.54.244; 7.AZ.54.243; 7.AZ.54.247; 7.AZ.55.157; 7.AZ.55.158; 7.AZ.55.196; 7.AZ.55.223; 7.AZ.55.240; 7.AZ.55.244; 7.AZ.55.243; 7.AZ.55.247; 7.AZ.56.157; 7.AZ.56.158; 7.AZ.56.196; 7.AZ.56.223; 7.AZ.56.240; 7.AZ.56.244; 7.AZ.56.243; 7.AZ.56.247; 7.AZ.157.157; 7.AZ.157.158; 7.AZ.157.196; 7.AZ.157.223; 7.AZ.157.240; 7.AZ.157.244; 7.AZ.157.243; 7.AZ.157.247; 7.AZ.196.157; 7.AZ.196.158; 7.AZ.196.196; 7.AZ.196.223; 7.AZ.196.240; 7.AZ.196.244; 7.AZ.196.243; 7.AZ.196.247; 7.AZ.223.157; 7.AZ.223.158; 7.AZ.223.196; 7.AZ.223.223; 7.AZ.223.240; 7.AZ.223.244; 7.AZ.223.243; 7.AZ.223.247; 7.AZ.240.157; 7.AZ.240.158; 7.AZ.240.196; 7.AZ.240.223; 7.AZ.240.240; 7.AZ.240.244; 7.AZ.240.243; 7.AZ.240.247; 7.AZ.244.157; 7.AZ.244.158; 7.AZ.244.196; 7.AZ.244.223; 7.AZ.244.240; 7.AZ.244.244; 7.AZ.244.243; 7.AZ.244.247; 7.AZ.247.157; 7.AZ.247.158; 7.AZ.247.196; 7.AZ.247.223; 7.AZ.247.240; 7.AZ.247.244; 7.AZ.247.243; 7.AZ.247.247;

Prodrugs of 7.BF

7.BF.4.157; 7.BF.4.158; 7.BF.4.196; 7.BF.4.223; 7.BF.4.240; 7.BF.4.244; 7.BF.4.243; 7.BF.4.247; 7.BF.5.157; 7.BF.5.158; 7.BF.5.196; 7.BF.5.223; 7.BF.5.240; 7.BF.5.244; 7.BF.5.243; 7.BF.5.247; 7.BF.7.157; 7.BF.7.158; 7.BF.7.196; 7.BF.7.223; 7.BF.7.240; 7.BF.7.244; 7.BF.7.243; 7.BF.7.247; 7.BF.15.157; 7.BF.15.158; 7.BF.15.196; 7.BF.15.223; 7.BF.15.240; 7.BF.15.244; 7.BF.15.243; 7.BF.15.247; 7.BF.16.157; 7.BF.16.158; 7.BF.16.196; 7.BF.16.223; 7.BF.16.240; 7.BF.16.244; 7.BF.16.243; 7.BF.16.247; 7.BF.18.157; 7.BF.18.158; 7.BF.18.196; 7.BF.18.223; 7.BF.18.240; 7.BF.18.244; 7.BF.18.243; 7.BF.18.247; 7.BF.26.157; 7.BF.26.158; 7.BF.26.196; 7.BF.26.223; 7.BF.26.240; 7.BF.26.244; 7.BF.26.243; 7.BF.26.247; 7.BF.27.157; 7.BF.27.158; 7.BF.27.196; 7.BF.27.223; 7.BF.27.240; 7.BF.27.244; 7.BF.27.243; 7.BF.27.247; 7.BF.29.157; 7.BF.29.158; 7.BF.29.196; 7.BF.29.223; 7.BF.29.240; 7.BF.29.244; 7.BF.29.243; 7.BF.29.247; 7.BF.54.157; 7.BF.54.158; 7.BF.54.196; 7.BF.54.223; 7.BF.54.240; 7.BF.54.244; 7.BF.54.243; 7.BF.54.247; 7.BF.55.157; 7.BF.55.158; 7.BF.55.196; 7.BF.55.223; 7.BF.55.240; 7.BF.55.244; 7.BF.55.243; 7.BF.55.247;

7.BF.56.157; 7.BF.56.158; 7.BF.56.196; 7.BF.56.223; 7.BF.56.240; 7.BF.56.244; 7.BF.56.243; 7.BF.56.247; 7.BF.157.157; 7.BF.157.158; 7.BF.157.196; 7.BF.157.223; 7.BF.157.240; 7.BF.157.244; 7.BF.157.243; 7.BF.157.247; 7.BF.196.157; 7.BF.196.158; 7.BF.196.196; 7.BF.196.223; 7.BF.196.240; 7.BF.196.244; 7.BF.196.243; 7.BF.196.247; 7.BF.223.157; 7.BF.223.158; 7.BF.223.196; 7.BF.223.223; 7.BF.223.240; 7.BF.223.244; 7.BF.223.243; 7.BF.223.247; 7.BF.240.157; 7.BF.240.158; 7.BF.240.196; 7.BF.240.223; 7.BF.240.240; 7.BF.240.244; 7.BF.240.243; 7.BF.240.247; 7.BF.244.157; 7.BF.244.158; 7.BF.244.196; 7.BF.244.223; 7.BF.244.240; 7.BF.244.244; 7.BF.244.243; 7.BF.244.247; 7.BF.247.157; 7.BF.247.158; 7.BF.247.196; 7.BF.247.223; 7.BF.247.240; 7.BF.247.244; 7.BF.247.243; 7.BF.247.247;

Prodrugs of 7.CI

7.CI.4.157; 7.CI.4.158; 7.CI.4.196; 7.CI.4.223; 7.CI.4.240; 7.CI.4.244; 7.CI.4.243; 7.CI.4.247; 7.CI.5.157; 7.CI.5.158; 7.CI.5.196; 7.CI.5.223; 7.CI.5.240; 7.CI.5.244; 7.CI.5.243; 7.CI.5.247; 7.CI.7.157; 7.CI.7.158; 7.CI.7.196; 7.CI.7.223; 7.CI.7.240; 7.CI.7.244; 7.CI.7.243; 7.CI.7.247; 7.CI.15.157; 7.CI.15.158; 7.CI.15.196; 7.CI.15.223; 7.CI.15.240; 7.CI.15.244; 7.CI.15.243; 7.CI.15.247; 7.CI.16.157; 7.CI.16.158; 7.CI.16.196; 7.CI.16.223; 7.CI.16.240; 7.CI.16.244; 7.CI.16.243; 7.CI.16.247; 7.CI.18.157; 7.CI.18.158; 7.CI.18.196; 7.CI.18.223; 7.CI.18.240; 7.CI.18.244; 7.CI.18.243; 7.CI.18.247; 7.CI.26.157; 7.CI.26.158; 7.CI.26.196; 7.CI.26.223; 7.CI.26.240; 7.CI.26.244; 7.CI.26.243; 7.CI.26.247; 7.CI.27.157; 7.CI.27.158; 7.CI.27.196; 7.CI.27.223; 7.CI.27.240; 7.CI.27.244; 7.CI.27.243; 7.CI.27.247; 7.CI.29.157; 7.CI.29.158; 7.CI.29.196; 7.CI.29.223; 7.CI.29.240; 7.CI.29.244; 7.CI.29.243; 7.CI.29.247; 7.CI.54.157; 7.CI.54.158; 7.CI.54.196; 7.CI.54.223; 7.CI.54.240; 7.CI.54.244; 7.CI.54.243; 7.CI.54.247; 7.CI.55.157; 7.CI.55.158; 7.CI.55.196; 7.CI.55.223; 7.CI.55.240; 7.CI.55.244; 7.CI.55.243; 7.CI.55.247; 7.CI.56.157; 7.CI.56.158; 7.CI.56.196; 7.CI.56.223; 7.CI.56.240; 7.CI.56.244; 7.CI.56.243; 7.CI.56.247; 7.CI.157.157; 7.CI.157.158; 7.CI.157.196; 7.CI.157.223; 7.CI.157.240; 7.CI.157.244; 7.CI.157.243; 7.CI.157.247; 7.CI.196.157; 7.CI.196.158; 7.CI.196.196; 7.CI.196.223; 7.CI.196.240; 7.CI.196.244; 7.CI.196.243; 7.CI.196.247; 7.CI.223.157; 7.CI.223.158; 7.CI.223.196; 7.CI.223.223; 7.CI.223.240; 7.CI.223.244; 7.CI.223.243; 7.CI.223.247; 7.CI.240.157; 7.CI.240.158; 7.CI.240.196; 7.CI.240.223; 7.CI.240.240; 7.CI.240.244; 7.CI.240.243; 7.CI.240.247; 7.CI.244.157; 7.CI.244.158; 7.CI.244.196; 7.CI.244.223; 7.CI.244.240; 7.CI.244.244; 7.CI.244.243; 7.CI.244.247; 7.CI.247.157; 7.CI.247.158; 7.CI.247.196; 7.CI.247.223; 7.CI.247.240; 7.CI.247.244; 7.CI.247.243; 7.CI.247.247;

Prodrugs of 7.CO

7.CO.4.157; 7.CO.4.158; 7.CO.4.196; 7.CO.4.223; 7.CO.4.240; 7.CO.4.244; 7.CO.4.243; 7.CO.4.247; 7.CO.5.157; 7.CO.5.158; 7.CO.5.196; 7.CO.5.223; 7.CO.5.240; 7.CO.5.244; 7.CO.5.243; 7.CO.5.247; 7.CO.7.157; 7.CO.7.158; 7.CO.7.196; 7.CO.7.223; 7.CO.7.240; 7.CO.7.244; 7.CO.7.243; 7.CO.7.247; 7.CO.15.157; 7.CO.15.158; 7.CO.15.196; 7.CO.15.223; 7.CO.15.240; 7.CO.15.244; 7.CO.15.243; 7.CO.15.247; 7.CO.16.157; 7.CO.16.158; 7.CO.16.196; 7.CO.16.223; 7.CO.16.240; 7.CO.16.244; 7.CO.16.243; 7.CO.16.247; 7.CO.18.157; 7.CO.18.158; 7.CO.18.196; 7.CO.18.223; 7.CO.18.240; 7.CO.18.244; 7.CO.18.243; 7.CO.18.247; 7.CO.26.157; 7.CO.26.158; 7.CO.26.196; 7.CO.26.223; 7.CO.26.240; 7.CO.26.244; 7.CO.26.243; 7.CO.26.247; 7.CO.27.157; 7.CO.27.158; 7.CO.27.196; 7.CO.27.223; 7.CO.27.240; 7.CO.27.244; 7.CO.27.243; 7.CO.27.247; 7.CO.29.157; 7.CO.29.158; 7.CO.29.196; 7.CO.29.223; 7.CO.29.240; 7.CO.29.244; 7.CO.29.243; 7.CO.29.247; 7.CO.54.157; 7.CO.54.158; 7.CO.54.196;

7.CO.54.223; 7.CO.54.240; 7.CO.54.244; 7.CO.54.243; 7.CO.54.247; 7.CO.55.157; 7.CO.55.158; 7.CO.55.196; 7.CO.55.223; 7.CO.55.240; 7.CO.55.244; 7.CO.55.243; 7.CO.55.247; 7.CO.56.157; 7.CO.56.158; 7.CO.56.196; 7.CO.56.223; 7.CO.56.240; 7.CO.56.244; 7.CO.56.243; 7.CO.56.247; 7.CO.157.157; 7.CO.157.158; 7.CO.157.196; 7.CO.157.223; 7.CO.157.240; 7.CO.157.244; 7.CO.157.243; 7.CO.157.247; 7.CO.196.157; 7.CO.196.158; 7.CO.196.196; 7.CO.196.223; 7.CO.196.240; 7.CO.196.244; 7.CO.196.243; 7.CO.196.247; 7.CO.223.157; 7.CO.223.158; 7.CO.223.196; 7.CO.223.223; 7.CO.223.240; 7.CO.223.244; 7.CO.223.243; 7.CO.223.247; 7.CO.240.157; 7.CO.240.158; 7.CO.240.196; 7.CO.240.223; 7.CO.240.240; 7.CO.240.244; 7.CO.240.243; 7.CO.240.247; 7.CO.244.157; 7.CO.244.158; 7.CO.244.196; 7.CO.244.223; 7.CO.244.240; 7.CO.244.244; 7.CO.244.243; 7.CO.244.247; 7.CO.4.157; 7.CO.4.158; 7.CO.4.196; 7.CO.4.223; 7.CO.4.240; 7.CO.4.244; 7.CO.4.243; 7.CO.4.247;

Prodrugs of 8.AH

8.AH.4.157; 8.AH.4.158; 8.AH.4.196; 8.AH.4.223; 8.AH.4.240; 8.AH.4.244; 8.AH.4.243; 8.AH.4.247; 8.AH.5.157; 8.AH.5.158; 8.AH.5.196; 8.AH.5.223; 8.AH.5.240; 8.AH.5.244; 8.AH.5.243; 8.AH.5.247; 8.AH.7.157; 8.AH.7.158; 8.AH.7.196; 8.AH.7.223; 8.AH.7.240; 8.AH.7.244; 8.AH.7.243; 8.AH.7.247; 8.AH.15.157; 8.AH.15.158; 8.AH.15.196; 8.AH.15.223; 8.AH.15.240; 8.AH.15.244; 8.AH.15.243; 8.AH.15.247; 8.AH.16.157; 8.AH.16.158; 8.AH.16.196; 8.AH.16.223; 8.AH.16.240; 8.AH.16.244; 8.AH.16.243; 8.AH.16.247; 8.AH.18.157; 8.AH.18.158; 8.AH.18.196; 8.AH.18.223; 8.AH.18.240; 8.AH.18.244; 8.AH.18.243; 8.AH.18.247; 8.AH.26.157; 8.AH.26.158; 8.AH.26.196; 8.AH.26.223; 8.AH.26.240; 8.AH.26.244; 8.AH.26.243; 8.AH.26.247; 8.AH.27.157; 8.AH.27.158; 8.AH.27.196; 8.AH.27.223; 8.AH.27.240; 8.AH.27.244; 8.AH.27.243; 8.AH.27.247; 8.AH.29.157; 8.AH.29.158; 8.AH.29.196; 8.AH.29.223; 8.AH.29.240; 8.AH.29.244; 8.AH.29.243; 8.AH.29.247; 8.AH.54.157; 8.AH.54.158; 8.AH.54.196; 8.AH.54.223; 8.AH.54.240; 8.AH.54.244; 8.AH.54.243; 8.AH.54.247; 8.AH.55.157; 8.AH.55.158; 8.AH.55.196; 8.AH.55.223; 8.AH.55.240; 8.AH.55.244; 8.AH.55.243; 8.AH.55.247; 8.AH.56.157; 8.AH.56.158; 8.AH.56.196; 8.AH.56.223; 8.AH.56.240; 8.AH.56.244; 8.AH.56.243; 8.AH.56.247; 8.AH.157.157; 8.AH.157.158; 8.AH.157.196; 8.AH.157.223; 8.AH.157.240; 8.AH.157.244; 8.AH.157.243; 8.AH.157.247; 8.AH.196.157; 8.AH.196.158; 8.AH.196.196; 8.AH.196.223; 8.AH.196.240; 8.AH.196.244; 8.AH.196.243; 8.AH.196.247; 8.AH.223.157; 8.AH.223.158; 8.AH.223.196; 8.AH.223.223; 8.AH.223.240; 8.AH.223.244; 8.AH.223.243; 8.AH.223.247; 8.AH.240.157; 8.AH.240.158; 8.AH.240.196; 8.AH.240.223; 8.AH.240.240; 8.AH.240.244; 8.AH.240.243; 8.AH.240.247; 8.AH.244.157; 8.AH.244.158; 8.AH.244.196; 8.AH.244.223; 8.AH.244.240; 8.AH.244.244; 8.AH.244.243; 8.AH.244.247; 8.AH.247.157; 8.AH.247.158; 8.AH.247.196; 8.AH.247.223; 8.AH.247.240; 8.AH.247.244; 8.AH.247.243; 8.AH.247.247;

Prodrugs of 8.AJ

8.AJ.4.157; 8.AJ.4.158; 8.AJ.4.196; 8.AJ.4.223; 8.AJ.4.240; 8.AJ.4.244; 8.AJ.4.243; 8.AJ.4.247; 8.AJ.5.157; 8.AJ.5.158; 8.AJ.5.196; 8.AJ.5.223; 8.AJ.5.240; 8.AJ.5.244; 8.AJ.5.243; 8.AJ.5.247; 8.AJ.7.157; 8.AJ.7.158; 8.AJ.7.196; 8.AJ.7.223; 8.AJ.7.240; 8.AJ.7.244; 8.AJ.7.243; 8.AJ.7.247; 8.AJ.15.157; 8.AJ.15.158; 8.AJ.15.196; 8.AJ.15.223; 8.AJ.15.240; 8.AJ.15.244; 8.AJ.15.243; 8.AJ.15.247; 8.AJ.16.157; 8.AJ.16.158; 8.AJ.16.196; 8.AJ.16.223; 8.AJ.16.240; 8.AJ.16.244; 8.AJ.16.243; 8.AJ.16.247; 8.AJ.18.157; 8.AJ.18.158; 8.AJ.18.196; 8.AJ.18.223; 8.AJ.18.240; 8.AJ.18.244; 8.AJ.18.243; 8.AJ.18.247; 8.AJ.26.157; 8.AJ.26.158; 8.AJ.26.196; 8.AJ.26.223; 8.AJ.26.240; 8.AJ.26.244; 8.AJ.26.243; 8.AJ.26.247;

8.AJ.27.157; 8.AJ.27.158; 8.AJ.27.196; 8.AJ.27.223; 8.AJ.27.240; 8.AJ.27.244; 8.AJ.27.243; 8.AJ.27.247; 8.AJ.29.157; 8.AJ.29.158; 8.AJ.29.196; 8.AJ.29.223; 8.AJ.29.240; 8.AJ.29.244; 8.AJ.29.243; 8.AJ.29.247; 8.AJ.54.157; 8.AJ.54.158; 8.AJ.54.196; 8.AJ.54.223; 8.AJ.54.240; 8.AJ.54.244; 8.AJ.54.243; 8.AJ.54.247; 8.AJ.55.157; 8.AJ.55.158; 8.AJ.55.196; 8.AJ.55.223; 8.AJ.55.240; 8.AJ.55.244; 8.AJ.55.243; 8.AJ.55.247; 8.AJ.56.157; 8.AJ.56.158; 8.AJ.56.196; 8.AJ.56.223; 8.AJ.56.240; 8.AJ.56.244; 8.AJ.56.243; 8.AJ.56.247; 8.AJ.157.157; 8.AJ.157.158; 8.AJ.157.196; 8.AJ.157.223; 8.AJ.157.240; 8.AJ.157.244; 8.AJ.157.243; 8.AJ.157.247; 8.AJ.196.157; 8.AJ.196.158; 8.AJ.196.196; 8.AJ.196.223; 8.AJ.196.240; 8.AJ.196.244; 8.AJ.196.243; 8.AJ.196.247; 8.AJ.223.157; 8.AJ.223.158; 8.AJ.223.196; 8.AJ.223.223; 8.AJ.223.240; 8.AJ.223.244; 8.AJ.223.243; 8.AJ.223.247; 8.AJ.240.157; 8.AJ.240.158; 8.AJ.240.196; 8.AJ.240.223; 8.AJ.240.240; 8.AJ.240.244; 8.AJ.240.243; 8.AJ.240.247; 8.AJ.244.157; 8.AJ.244.158; 8.AJ.244.196; 8.AJ.244.223; 8.AJ.244.240; 8.AJ.244.244; 8.AJ.244.243; 8.AJ.244.247; 8.AJ.247.157; 8.AJ.247.158; 8.AJ.247.196; 8.AJ.247.223; 8.AJ.247.240; 8.AJ.247.244; 8.AJ.247.243; 8.AJ.247.247;

Prodrugs of 8.AN

8.AN.4.157; 8.AN.4.158; 8.AN.4.196; 8.AN.4.223; 8.AN.4.240; 8.AN.4.244; 8.AN.4.243; 8.AN.4.247; 8.AN.5.157; 8.AN.5.158; 8.AN.5.196; 8.AN.5.223; 8.AN.5.240; 8.AN.5.244; 8.AN.5.243; 8.AN.5.247; 8.AN.7.157; 8.AN.7.158; 8.AN.7.196; 8.AN.7.223; 8.AN.7.240; 8.AN.7.244; 8.AN.7.243; 8.AN.7.247; 8.AN.15.157; 8.AN.15.158; 8.AN.15.196; 8.AN.15.223; 8.AN.15.240; 8.AN.15.244; 8.AN.15.243; 8.AN.15.247; 8.AN.16.157; 8.AN.16.158; 8.AN.16.196; 8.AN.16.223; 8.AN.16.240; 8.AN.16.244; 8.AN.16.243; 8.AN.16.247; 8.AN.18.157; 8.AN.18.158; 8.AN.18.196; 8.AN.18.223; 8.AN.18.240; 8.AN.18.244; 8.AN.18.243; 8.AN.18.247; 8.AN.26.157; 8.AN.26.158; 8.AN.26.196; 8.AN.26.223; 8.AN.26.240; 8.AN.26.244; 8.AN.26.243; 8.AN.26.247; 8.AN.27.157; 8.AN.27.158; 8.AN.27.196; 8.AN.27.223; 8.AN.27.240; 8.AN.27.244; 8.AN.27.243; 8.AN.27.247; 8.AN.29.157; 8.AN.29.158; 8.AN.29.196; 8.AN.29.223; 8.AN.29.240; 8.AN.29.244; 8.AN.29.243; 8.AN.29.247; 8.AN.54.157; 8.AN.54.158; 8.AN.54.196; 8.AN.54.223; 8.AN.54.240; 8.AN.54.244; 8.AN.54.243; 8.AN.54.247; 8.AN.55.157; 8.AN.55.158; 8.AN.55.196; 8.AN.55.223; 8.AN.55.240; 8.AN.55.244; 8.AN.55.243; 8.AN.55.247; 8.AN.56.157; 8.AN.56.158; 8.AN.56.196; 8.AN.56.223; 8.AN.56.240; 8.AN.56.244; 8.AN.56.243; 8.AN.56.247; 8.AN.157.157; 8.AN.157.158; 8.AN.157.196; 8.AN.157.223; 8.AN.157.240; 8.AN.157.244; 8.AN.157.243; 8.AN.157.247; 8.AN.196.157; 8.AN.196.158; 8.AN.196.196; 8.AN.196.223; 8.AN.196.240; 8.AN.196.244; 8.AN.196.243; 8.AN.196.247; 8.AN.223.157; 8.AN.223.158; 8.AN.223.196; 8.AN.223.223; 8.AN.223.240; 8.AN.223.244; 8.AN.223.243; 8.AN.223.247; 8.AN.240.157; 8.AN.240.158; 8.AN.240.196; 8.AN.240.223; 8.AN.240.240; 8.AN.240.244; 8.AN.240.243; 8.AN.240.247; 8.AN.244.157; 8.AN.244.158; 8.AN.244.196; 8.AN.244.223; 8.AN.244.240; 8.AN.244.244; 8.AN.244.243; 8.AN.244.247; 8.AN.247.157; 8.AN.247.158; 8.AN.247.196; 8.AN.247.223; 8.AN.247.240; 8.AN.247.244; 8.AN.247.243; 8.AN.247.247;

Prodrugs of 8.AP

8.AP.4.157; 8.AP.4.158; 8.AP.4.196; 8.AP.4.223; 8.AP.4.240; 8.AP.4.244; 8.AP.4.243; 8.AP.4.247; 8.AP.5.157; 8.AP.5.158; 8.AP.5.196; 8.AP.5.223; 8.AP.5.240; 8.AP.5.244; 8.AP.5.243; 8.AP.5.247; 8.AP.7.157; 8.AP.7.158; 8.AP.7.196; 8.AP.7.223; 8.AP.7.240; 8.AP.7.244; 8.AP.7.243; 8.AP.7.247; 8.AP.15.157; 8.AP.15.158; 8.AP.15.196; 8.AP.15.223; 8.AP.15.240; 8.AP.15.244; 8.AP.15.243; 8.AP.15.247; 8.AP.16.157; 8.AP.16.158; 8.AP.16.196; 8.AP.16.223; 8.AP.16.240; 8.AP.16.244; 8.AP.16.243; 8.AP.16.247;

8.AP.18.157; 8.AP.18.158; 8.AP.18.196; 8.AP.18.223; 8.AP.18.240; 8.AP.18.244; 8.AP.18.243; 8.AP.18.247; 8.AP.26.157; 8.AP.26.158; 8.AP.26.196; 8.AP.26.223; 8.AP.26.240; 8.AP.26.244; 8.AP.26.243; 8.AP.26.247; 8.AP.27.157; 8.AP.27.158; 8.AP.27.196; 8.AP.27.223; 8.AP.27.240; 8.AP.27.244; 8.AP.27.243; 8.AP.27.247; 8.AP.29.157; 8.AP.29.158; 8.AP.29.196; 8.AP.29.223; 8.AP.29.240; 8.AP.29.244; 8.AP.29.243; 8.AP.29.247; 8.AP.54.157; 8.AP.54.158; 8.AP.54.196; 8.AP.54.223; 8.AP.54.240; 8.AP.54.244; 8.AP.54.243; 8.AP.54.247; 8.AP.55.157; 8.AP.55.158; 8.AP.55.196; 8.AP.55.223; 8.AP.55.240; 8.AP.55.244; 8.AP.55.243; 8.AP.55.247; 8.AP.56.157; 8.AP.56.158; 8.AP.56.196; 8.AP.56.223; 8.AP.56.240; 8.AP.56.244; 8.AP.56.243; 8.AP.56.247; 8.AP.157.157; 8.AP.157.158; 8.AP.157.196; 8.AP.157.223; 8.AP.157.240; 8.AP.157.244; 8.AP.157.243; 8.AP.157.247; 8.AP.196.157; 8.AP.196.158; 8.AP.196.196; 8.AP.196.223; 8.AP.196.240; 8.AP.196.244; 8.AP.196.243; 8.AP.196.247; 8.AP.223.157; 8.AP.223.158; 8.AP.223.196; 8.AP.223.223; 8.AP.223.240; 8.AP.223.244; 8.AP.223.243; 8.AP.223.247; 8.AP.240.157; 8.AP.240.158; 8.AP.240.196; 8.AP.240.223; 8.AP.240.240; 8.AP.240.244; 8.AP.240.243; 8.AP.240.247; 8.AP.244.157; 8.AP.244.158; 8.AP.244.196; 8.AP.244.223; 8.AP.244.240; 8.AP.244.244; 8.AP.244.243; 8.AP.244.247; 8.AP.247.157; 8.AP.247.158; 8.AP.247.196; 8.AP.247.223; 8.AP.247.240; 8.AP.247.244; 8.AP.247.243; 8.AP.247.247;

Prodrugs of 8.AZ

8.AZ.4.157; 8.AZ.4.158; 8.AZ.4.196; 8.AZ.4.223; 8.AZ.4.240; 8.AZ.4.244; 8.AZ.4.243; 8.AZ.4.247; 8.AZ.5.157; 8.AZ.5.158; 8.AZ.5.196; 8.AZ.5.223; 8.AZ.5.240; 8.AZ.5.244; 8.AZ.5.243; 8.AZ.5.247; 8.AZ.7.157; 8.AZ.7.158; 8.AZ.7.196; 8.AZ.7.223; 8.AZ.7.240; 8.AZ.7.244; 8.AZ.7.243; 8.AZ.7.247; 8.AZ.15.157; 8.AZ.15.158; 8.AZ.15.196; 8.AZ.15.223; 8.AZ.15.240; 8.AZ.15.244; 8.AZ.15.243; 8.AZ.15.247; 8.AZ.16.157; 8.AZ.16.158; 8.AZ.16.196; 8.AZ.16.223; 8.AZ.16.240; 8.AZ.16.244; 8.AZ.16.243; 8.AZ.16.247; 8.AZ.18.157; 8.AZ.18.158; 8.AZ.18.196; 8.AZ.18.223; 8.AZ.18.240; 8.AZ.18.244; 8.AZ.18.243; 8.AZ.18.247; 8.AZ.26.157; 8.AZ.26.158; 8.AZ.26.196; 8.AZ.26.223; 8.AZ.26.240; 8.AZ.26.244; 8.AZ.26.243; 8.AZ.26.247; 8.AZ.27.157; 8.AZ.27.158; 8.AZ.27.196; 8.AZ.27.223; 8.AZ.27.240; 8.AZ.27.244; 8.AZ.27.243; 8.AZ.27.247; 8.AZ.29.157; 8.AZ.29.158; 8.AZ.29.196; 8.AZ.29.223; 8.AZ.29.240; 8.AZ.29.244; 8.AZ.29.243; 8.AZ.29.247; 8.AZ.54.157; 8.AZ.54.158; 8.AZ.54.196; 8.AZ.54.223; 8.AZ.54.240; 8.AZ.54.244; 8.AZ.54.243; 8.AZ.54.247; 8.AZ.55.157; 8.AZ.55.158; 8.AZ.55.196; 8.AZ.55.223; 8.AZ.55.240; 8.AZ.55.244; 8.AZ.55.243; 8.AZ.55.247; 8.AZ.56.157; 8.AZ.56.158; 8.AZ.56.196; 8.AZ.56.223; 8.AZ.56.240; 8.AZ.56.244; 8.AZ.56.243; 8.AZ.56.247; 8.AZ.157.157; 8.AZ.157.158; 8.AZ.157.196; 8.AZ.157.223; 8.AZ.157.240; 8.AZ.157.244; 8.AZ.157.243; 8.AZ.157.247; 8.AZ.196.157; 8.AZ.196.158; 8.AZ.196.196; 8.AZ.196.223; 8.AZ.196.240; 8.AZ.196.244; 8.AZ.196.243; 8.AZ.196.247; 8.AZ.223.157; 8.AZ.223.158; 8.AZ.223.196; 8.AZ.223.223; 8.AZ.223.240; 8.AZ.223.244; 8.AZ.223.243; 8.AZ.223.247; 8.AZ.240.157; 8.AZ.240.158; 8.AZ.240.196; 8.AZ.240.223; 8.AZ.240.240; 8.AZ.240.244; 8.AZ.240.243; 8.AZ.240.247; 8.AZ.244.157; 8.AZ.244.158; 8.AZ.244.196; 8.AZ.244.223; 8.AZ.244.240; 8.AZ.244.244; 8.AZ.244.243; 8.AZ.244.247; 8.AZ.247.157; 8.AZ.247.158; 8.AZ.247.196; 8.AZ.247.223; 8.AZ.247.240; 8.AZ.247.244; 8.AZ.247.243; 8.AZ.247.247;

Prodrugs of 8.BF

8.BF.4.157; 8.BF.4.158; 8.BF.4.196; 8.BF.4.223; 8.BF.4.240; 8.BF.4.244; 8.BF.4.243; 8.BF.4.247; 8.BF.5.157; 8.BF.5.158; 8.BF.5.196; 8.BF.5.223; 8.BF.5.240; 8.BF.5.244;

8.BF.5.243; 8.BF.5.247; 8.BF.7.157; 8.BF.7.158; 8.BF.7.196; 8.BF.7.223; 8.BF.7.240; 8.BF.7.244; 8.BF.7.243; 8.BF.7.247; 8.BF.15.157; 8.BF.15.158; 8.BF.15.196; 8.BF.15.223; 8.BF.15.240; 8.BF.15.244; 8.BF.15.243; 8.BF.15.247; 8.BF.16.157; 8.BF.16.158; 8.BF.16.196; 8.BF.16.223; 8.BF.16.240; 8.BF.16.244; 8.BF.16.243; 8.BF.16.247; 8.BF.18.157; 8.BF.18.158; 8.BF.18.196; 8.BF.18.223; 8.BF.18.240; 8.BF.18.244; 8.BF.18.243; 8.BF.18.247; 8.BF.26.157; 8.BF.26.158; 8.BF.26.196; 8.BF.26.223; 8.BF.26.240; 8.BF.26.244; 8.BF.26.243; 8.BF.26.247; 8.BF.27.157; 8.BF.27.158; 8.BF.27.196; 8.BF.27.223; 8.BF.27.240; 8.BF.27.244; 8.BF.27.243; 8.BF.27.247; 8.BF.29.157; 8.BF.29.158; 8.BF.29.196; 8.BF.29.223; 8.BF.29.240; 8.BF.29.244; 8.BF.29.243; 8.BF.29.247; 8.BF.54.157; 8.BF.54.158; 8.BF.54.196; 8.BF.54.223; 8.BF.54.240; 8.BF.54.244; 8.BF.54.243; 8.BF.54.247; 8.BF.55.157; 8.BF.55.158; 8.BF.55.196; 8.BF.55.223; 8.BF.55.240; 8.BF.55.244; 8.BF.55.243; 8.BF.55.247; 8.BF.56.157; 8.BF.56.158; 8.BF.56.196; 8.BF.56.223; 8.BF.56.240; 8.BF.56.244; 8.BF.56.243; 8.BF.56.247; 8.BF.157.157; 8.BF.157.158; 8.BF.157.196; 8.BF.157.223; 8.BF.157.240; 8.BF.157.244; 8.BF.157.243; 8.BF.157.247; 8.BF.196.157; 8.BF.196.158; 8.BF.196.196; 8.BF.196.223; 8.BF.196.240; 8.BF.196.244; 8.BF.196.243; 8.BF.196.247; 8.BF.223.157; 8.BF.223.158; 8.BF.223.196; 8.BF.223.223; 8.BF.223.240; 8.BF.223.244; 8.BF.223.243; 8.BF.223.247; 8.BF.240.157; 8.BF.240.158; 8.BF.240.196; 8.BF.240.223; 8.BF.240.240; 8.BF.240.244; 8.BF.240.243; 8.BF.240.247; 8.BF.244.157; 8.BF.244.158; 8.BF.244.196; 8.BF.244.223; 8.BF.244.240; 8.BF.244.244; 8.BF.244.243; 8.BF.244.247; 8.BF.247.157; 8.BF.247.158; 8.BF.247.196; 8.BF.247.223; 8.BF.247.240; 8.BF.247.244; 8.BF.247.243; 8.BF.247.247;

Prodrugs of 8.CI

8.CI.4.157; 8.CI.4.158; 8.CI.4.196; 8.CI.4.223; 8.CI.4.240; 8.CI.4.244; 8.CI.4.243; 8.CI.4.247; 8.CI.5.157; 8.CI.5.158; 8.CI.5.196; 8.CI.5.223; 8.CI.5.240; 8.CI.5.244; 8.CI.5.243; 8.CI.5.247; 8.CI.7.157; 8.CI.7.158; 8.CI.7.196; 8.CI.7.223; 8.CI.7.240; 8.CI.7.244; 8.CI.7.243; 8.CI.7.247; 8.CI.15.157; 8.CI.15.158; 8.CI.15.196; 8.CI.15.223; 8.CI.15.240; 8.CI.15.244; 8.CI.15.243; 8.CI.15.247; 8.CI.16.157; 8.CI.16.158; 8.CI.16.196; 8.CI.16.223; 8.CI.16.240; 8.CI.16.244; 8.CI.16.243; 8.CI.16.247; 8.CI.18.157; 8.CI.18.158; 8.CI.18.196; 8.CI.18.223; 8.CI.18.240; 8.CI.18.244; 8.CI.18.243; 8.CI.18.247; 8.CI.26.157; 8.CI.26.158; 8.CI.26.196; 8.CI.26.223; 8.CI.26.240; 8.CI.26.244; 8.CI.26.243; 8.CI.26.247; 8.CI.27.157; 8.CI.27.158; 8.CI.27.196; 8.CI.27.223; 8.CI.27.240; 8.CI.27.244; 8.CI.27.243; 8.CI.27.247; 8.CI.29.157; 8.CI.29.158; 8.CI.29.196; 8.CI.29.223; 8.CI.29.240; 8.CI.29.244; 8.CI.29.243; 8.CI.29.247; 8.CI.54.157; 8.CI.54.158; 8.CI.54.196; 8.CI.54.223; 8.CI.54.240; 8.CI.54.244; 8.CI.54.243; 8.CI.54.247; 8.CI.55.157; 8.CI.55.158; 8.CI.55.196; 8.CI.55.223; 8.CI.55.240; 8.CI.55.244; 8.CI.55.243; 8.CI.55.247; 8.CI.56.157; 8.CI.56.158; 8.CI.56.196; 8.CI.56.223; 8.CI.56.240; 8.CI.56.244; 8.CI.56.243; 8.CI.56.247; 8.CI.157.157; 8.CI.157.158; 8.CI.157.196; 8.CI.157.223; 8.CI.157.240; 8.CI.157.244; 8.CI.157.243; 8.CI.157.247; 8.CI.196.157; 8.CI.196.158; 8.CI.196.196; 8.CI.196.223; 8.CI.196.240; 8.CI.196.244; 8.CI.196.243; 8.CI.196.247; 8.CI.223.157; 8.CI.223.158; 8.CI.223.196; 8.CI.223.223; 8.CI.223.240; 8.CI.223.244; 8.CI.223.243; 8.CI.223.247; 8.CI.240.157; 8.CI.240.158; 8.CI.240.196; 8.CI.240.223; 8.CI.240.240; 8.CI.240.244; 8.CI.240.243; 8.CI.240.247; 8.CI.244.157; 8.CI.244.158; 8.CI.244.196; 8.CI.244.223; 8.CI.244.240; 8.CI.244.244; 8.CI.244.243; 8.CI.244.247; 8.CI.247.157; 8.CI.247.158; 8.CI.247.196; 8.CI.247.223; 8.CI.247.240; 8.CI.247.244; 8.CI.247.243; 8.CI.247.247;

Prodrugs of 8.CO

8.CO.4.157; 8.CO.4.158; 8.CO.4.196; 8.CO.4.223; 8.CO.4.240; 8.CO.4.244; 8.CO.4.243; 8.CO.4.247; 8.CO.5.157; 8.CO.5.158; 8.CO.5.196; 8.CO.5.223; 8.CO.5.240; 8.CO.5.244; 8.CO.5.243; 8.CO.5.247; 8.CO.7.157; 8.CO.7.158; 8.CO.7.196; 8.CO.7.223; 8.CO.7.240; 8.CO.7.244; 8.CO.7.243; 8.CO.7.247; 8.CO.15.157; 8.CO.15.158; 8.CO.15.196; 8.CO.15.223; 8.CO.15.240; 8.CO.15.244; 8.CO.15.243; 8.CO.15.247; 8.CO.16.157; 8.CO.16.158; 8.CO.16.196; 8.CO.16.223; 8.CO.16.240; 8.CO.16.244; 8.CO.16.243; 8.CO.16.247; 8.CO.18.157; 8.CO.18.158; 8.CO.18.196; 8.CO.18.223; 8.CO.18.240; 8.CO.18.244; 8.CO.18.243; 8.CO.18.247; 8.CO.26.157; 8.CO.26.158; 8.CO.26.196; 8.CO.26.223; 8.CO.26.240; 8.CO.26.244; 8.CO.26.243; 8.CO.26.247; 8.CO.27.157; 8.CO.27.158; 8.CO.27.196; 8.CO.27.223; 8.CO.27.240; 8.CO.27.244; 8.CO.27.243; 8.CO.27.247; 8.CO.29.157; 8.CO.29.158; 8.CO.29.196; 8.CO.29.223; 8.CO.29.240; 8.CO.29.244; 8.CO.29.243; 8.CO.29.247; 8.CO.54.157; 8.CO.54.158; 8.CO.54.196; 8.CO.54.223; 8.CO.54.240; 8.CO.54.244; 8.CO.54.243; 8.CO.54.247; 8.CO.55.157; 8.CO.55.158; 8.CO.55.196; 8.CO.55.223; 8.CO.55.240; 8.CO.55.244; 8.CO.55.243; 8.CO.55.247; 8.CO.56.157; 8.CO.56.158; 8.CO.56.196; 8.CO.56.223; 8.CO.56.240; 8.CO.56.244; 8.CO.56.243; 8.CO.56.247; 8.CO.157.157; 8.CO.157.158; 8.CO.157.196; 8.CO.157.223; 8.CO.157.240; 8.CO.157.244; 8.CO.157.243; 8.CO.157.247; 8.CO.196.157; 8.CO.196.158; 8.CO.196.196; 8.CO.196.223; 8.CO.196.240; 8.CO.196.244; 8.CO.196.243; 8.CO.196.247; 8.CO.223.157; 8.CO.223.158; 8.CO.223.196; 8.CO.223.223; 8.CO.223.240; 8.CO.223.244; 8.CO.223.243; 8.CO.223.247; 8.CO.240.157; 8.CO.240.158; 8.CO.240.196; 8.CO.240.223; 8.CO.240.240; 8.CO.240.244; 8.CO.240.243; 8.CO.240.247; 8.CO.244.157; 8.CO.244.158; 8.CO.244.196; 8.CO.244.223; 8.CO.244.240; 8.CO.244.244; 8.CO.244.243; 8.CO.244.247; 8.CO.247.157; 8.CO.247.158; 8.CO.247.196; 8.CO.247.223; 8.CO.247.240; 8.CO.247.244; 8.CO.247.243; 8.CO.247.247;

Prodrugs of 9.AH

9.AH.4.157; 9.AH.4.158; 9.AH.4.196; 9.AH.4.223; 9.AH.4.240; 9.AH.4.244; 9.AH.4.243; 9.AH.4.247; 9.AH.5.157; 9.AH.5.158; 9.AH.5.196; 9.AH.5.223; 9.AH.5.240; 9.AH.5.244; 9.AH.5.243; 9.AH.5.247; 9.AH.7.157; 9.AH.7.158; 9.AH.7.196; 9.AH.7.223; 9.AH.7.240; 9.AH.7.244; 9.AH.7.243; 9.AH.7.247; 9.AH.15.157; 9.AH.15.158; 9.AH.15.196; 9.AH.15.223; 9.AH.15.240; 9.AH.15.244; 9.AH.15.243; 9.AH.15.247; 9.AH.16.157; 9.AH.16.158; 9.AH.16.196; 9.AH.16.223; 9.AH.16.240; 9.AH.16.244; 9.AH.16.243; 9.AH.16.247; 9.AH.18.157; 9.AH.18.158; 9.AH.18.196; 9.AH.18.223; 9.AH.18.240; 9.AH.18.244; 9.AH.18.243; 9.AH.18.247; 9.AH.26.157; 9.AH.26.158; 9.AH.26.196; 9.AH.26.223; 9.AH.26.240; 9.AH.26.244; 9.AH.26.243; 9.AH.26.247; 9.AH.27.157; 9.AH.27.158; 9.AH.27.196; 9.AH.27.223; 9.AH.27.240; 9.AH.27.244; 9.AH.27.243; 9.AH.27.247; 9.AH.29.157; 9.AH.29.158; 9.AH.29.196; 9.AH.29.223; 9.AH.29.240; 9.AH.29.244; 9.AH.29.243; 9.AH.29.247; 9.AH.54.157; 9.AH.54.158; 9.AH.54.196; 9.AH.54.223; 9.AH.54.240; 9.AH.54.244; 9.AH.54.243; 9.AH.54.247; 9.AH.55.157; 9.AH.55.158; 9.AH.55.196; 9.AH.55.223; 9.AH.55.240; 9.AH.55.244; 9.AH.55.243; 9.AH.55.247; 9.AH.56.157; 9.AH.56.158; 9.AH.56.196; 9.AH.56.223; 9.AH.56.240; 9.AH.56.244; 9.AH.56.243; 9.AH.56.247; 9.AH.157.157; 9.AH.157.158; 9.AH.157.196; 9.AH.157.223; 9.AH.157.240; 9.AH.157.244; 9.AH.157.243; 9.AH.157.247; 9.AH.196.157; 9.AH.196.158; 9.AH.196.196; 9.AH.196.223; 9.AH.196.240; 9.AH.196.244; 9.AH.196.243; 9.AH.196.247; 9.AH.223.157; 9.AH.223.158; 9.AH.223.196; 9.AH.223.223; 9.AH.223.240; 9.AH.223.244; 9.AH.223.243; 9.AH.223.247; 9.AH.240.157; 9.AH.240.158; 9.AH.240.196; 9.AH.240.223; 9.AH.240.240; 9.AH.240.244; 9.AH.240.243; 9.AH.240.247; 9.AH.244.157; 9.AH.244.158; 9.AH.244.196; 9.AH.244.223; 9.AH.244.240; 9.AH.244.244; 9.AH.244.243;

9.AH.244.247; 9.AH.247.157; 9.AH.247.158; 9.AH.247.196; 9.AH.247.223; 9.AH.247.240; 9.AH.247.244; 9.AH.247.243; 9.AH.247.247;

Prodrugs of 9.AJ

9.AJ.4.157; 9.AJ.4.158; 9.AJ.4.196; 9.AJ.4.223; 9.AJ.4.240; 9.AJ.4.244; 9.AJ.4.243; 9.AJ.4.247; 9.AJ.5.157; 9.AJ.5.158; 9.AJ.5.196; 9.AJ.5.223; 9.AJ.5.240; 9.AJ.5.244; 9.AJ.5.243; 9.AJ.5.247; 9.AJ.7.157; 9.AJ.7.158; 9.AJ.7.196; 9.AJ.7.223; 9.AJ.7.240; 9.AJ.7.244; 9.AJ.7.243; 9.AJ.7.247; 9.AJ.15.157; 9.AJ.15.158; 9.AJ.15.196; 9.AJ.15.223; 9.AJ.15.240; 9.AJ.15.244; 9.AJ.15.243; 9.AJ.15.247; 9.AJ.16.157; 9.AJ.16.158; 9.AJ.16.196; 9.AJ.16.223; 9.AJ.16.240; 9.AJ.16.244; 9.AJ.16.243; 9.AJ.16.247; 9.AJ.18.157; 9.AJ.18.158; 9.AJ.18.196; 9.AJ.18.223; 9.AJ.18.240; 9.AJ.18.244; 9.AJ.18.243; 9.AJ.18.247; 9.AJ.26.157; 9.AJ.26.158; 9.AJ.26.196; 9.AJ.26.223; 9.AJ.26.240; 9.AJ.26.244; 9.AJ.26.243; 9.AJ.26.247; 9.AJ.27.157; 9.AJ.27.158; 9.AJ.27.196; 9.AJ.27.223; 9.AJ.27.240; 9.AJ.27.244; 9.AJ.27.243; 9.AJ.27.247; 9.AJ.29.157; 9.AJ.29.158; 9.AJ.29.196; 9.AJ.29.223; 9.AJ.29.240; 9.AJ.29.244; 9.AJ.29.243; 9.AJ.29.247; 9.AJ.54.157; 9.AJ.54.158; 9.AJ.54.196; 9.AJ.54.223; 9.AJ.54.240; 9.AJ.54.244; 9.AJ.54.243; 9.AJ.54.247; 9.AJ.55.157; 9.AJ.55.158; 9.AJ.55.196; 9.AJ.55.223; 9.AJ.55.240; 9.AJ.55.244; 9.AJ.55.243; 9.AJ.55.247; 9.AJ.56.157; 9.AJ.56.158; 9.AJ.56.196; 9.AJ.56.223; 9.AJ.56.240; 9.AJ.56.244; 9.AJ.56.243; 9.AJ.56.247; 9.AJ.157.157; 9.AJ.157.158; 9.AJ.157.196; 9.AJ.157.223; 9.AJ.157.240; 9.AJ.157.244; 9.AJ.157.243; 9.AJ.157.247; 9.AJ.196.157; 9.AJ.196.158; 9.AJ.196.196; 9.AJ.196.223; 9.AJ.196.240; 9.AJ.196.244; 9.AJ.196.243; 9.AJ.196.247; 9.AJ.223.157; 9.AJ.223.158; 9.AJ.223.196; 9.AJ.223.223; 9.AJ.223.240; 9.AJ.223.244; 9.AJ.223.243; 9.AJ.223.247; 9.AJ.240.157; 9.AJ.240.158; 9.AJ.240.196; 9.AJ.240.223; 9.AJ.240.240; 9.AJ.240.244; 9.AJ.240.243; 9.AJ.240.247; 9.AJ.244.157; 9.AJ.244.158; 9.AJ.244.196; 9.AJ.244.223; 9.AJ.244.240; 9.AJ.244.244; 9.AJ.244.243; 9.AJ.244.247; 9.AJ.247.157; 9.AJ.247.158; 9.AJ.247.196; 9.AJ.247.223; 9.AJ.247.240; 9.AJ.247.244; 9.AJ.247.243; 9.AJ.247.247;

Prodrugs of 9.AN

9.AN.4.157; 9.AN.4.158; 9.AN.4.196; 9.AN.4.223; 9.AN.4.240; 9.AN.4.244; 9.AN.4.243; 9.AN.4.247; 9.AN.5.157; 9.AN.5.158; 9.AN.5.196; 9.AN.5.223; 9.AN.5.240; 9.AN.5.244; 9.AN.5.243; 9.AN.5.247; 9.AN.7.157; 9.AN.7.158; 9.AN.7.196; 9.AN.7.223; 9.AN.7.240; 9.AN.7.244; 9.AN.7.243; 9.AN.7.247; 9.AN.15.157; 9.AN.15.158; 9.AN.15.196; 9.AN.15.223; 9.AN.15.240; 9.AN.15.244; 9.AN.15.243; 9.AN.15.247; 9.AN.16.157; 9.AN.16.158; 9.AN.16.196; 9.AN.16.223; 9.AN.16.240; 9.AN.16.244; 9.AN.16.243; 9.AN.16.247; 9.AN.18.157; 9.AN.18.158; 9.AN.18.196; 9.AN.18.223; 9.AN.18.240; 9.AN.18.244; 9.AN.18.243; 9.AN.18.247; 9.AN.26.157; 9.AN.26.158; 9.AN.26.196; 9.AN.26.223; 9.AN.26.240; 9.AN.26.244; 9.AN.26.243; 9.AN.26.247; 9.AN.27.157; 9.AN.27.158; 9.AN.27.196; 9.AN.27.223; 9.AN.27.240; 9.AN.27.244; 9.AN.27.243; 9.AN.27.247; 9.AN.29.157; 9.AN.29.158; 9.AN.29.196; 9.AN.29.223; 9.AN.29.240; 9.AN.29.244; 9.AN.29.243; 9.AN.29.247; 9.AN.54.157; 9.AN.54.158; 9.AN.54.196; 9.AN.54.223; 9.AN.54.240; 9.AN.54.244; 9.AN.54.243; 9.AN.54.247; 9.AN.55.157; 9.AN.55.158; 9.AN.55.196; 9.AN.55.223; 9.AN.55.240; 9.AN.55.244; 9.AN.55.243; 9.AN.55.247; 9.AN.56.157; 9.AN.56.158; 9.AN.56.196; 9.AN.56.223; 9.AN.56.240; 9.AN.56.244; 9.AN.56.243; 9.AN.56.247; 9.AN.157.157; 9.AN.157.158; 9.AN.157.196; 9.AN.157.223; 9.AN.157.240; 9.AN.157.244; 9.AN.157.243; 9.AN.157.247; 9.AN.196.157; 9.AN.196.158; 9.AN.196.196; 9.AN.196.223; 9.AN.196.240; 9.AN.196.244; 9.AN.196.243; 9.AN.196.247; 9.AN.223.157; 9.AN.223.158; 9.AN.223.196; 9.AN.223.223; 9.AN.223.240; 9.AN.223.244; 9.AN.223.243; 9.AN.223.247; 9.AN.240.157; 9.AN.240.158; 9.AN.240.196;

9.AN.240.223; 9.AN.240.240; 9.AN.240.244; 9.AN.240.243; 9.AN.240.247; 9.AN.244.157; 9.AN.244.158; 9.AN.244.196; 9.AN.244.223; 9.AN.244.240; 9.AN.244.244; 9.AN.244.243; 9.AN.244.247; 9.AN.247.157; 9.AN.247.158; 9.AN.247.196; 9.AN.247.223; 9.AN.247.240; 9.AN.247.244; 9.AN.247.243; 9.AN.247.247;

Prodrugs of 9.AP

9.AP.4.157; 9.AP.4.158; 9.AP.4.196; 9.AP.4.223; 9.AP.4.240; 9.AP.4.244; 9.AP.4.243; 9.AP.4.247; 9.AP.5.157; 9.AP.5.158; 9.AP.5.196; 9.AP.5.223; 9.AP.5.240; 9.AP.5.244; 9.AP.5.243; 9.AP.5.247; 9.AP.7.157; 9.AP.7.158; 9.AP.7.196; 9.AP.7.223; 9.AP.7.240; 9.AP.7.244; 9.AP.7.243; 9.AP.7.247; 9.AP.15.157; 9.AP.15.158; 9.AP.15.196; 9.AP.15.223; 9.AP.15.240; 9.AP.15.244; 9.AP.15.243; 9.AP.15.247; 9.AP.16.157; 9.AP.16.158; 9.AP.16.196; 9.AP.16.223; 9.AP.16.240; 9.AP.16.244; 9.AP.16.243; 9.AP.16.247; 9.AP.18.157; 9.AP.18.158; 9.AP.18.196; 9.AP.18.223; 9.AP.18.240; 9.AP.18.244; 9.AP.18.243; 9.AP.18.247; 9.AP.26.157; 9.AP.26.158; 9.AP.26.196; 9.AP.26.223; 9.AP.26.240; 9.AP.26.244; 9.AP.26.243; 9.AP.26.247; 9.AP.27.157; 9.AP.27.158; 9.AP.27.196; 9.AP.27.223; 9.AP.27.240; 9.AP.27.244; 9.AP.27.243; 9.AP.27.247; 9.AP.29.157; 9.AP.29.158; 9.AP.29.196; 9.AP.29.223; 9.AP.29.240; 9.AP.29.244; 9.AP.29.243; 9.AP.29.247; 9.AP.54.157; 9.AP.54.158; 9.AP.54.196; 9.AP.54.223; 9.AP.54.240; 9.AP.54.244; 9.AP.54.243; 9.AP.54.247; 9.AP.55.157; 9.AP.55.158; 9.AP.55.196; 9.AP.55.223; 9.AP.55.240; 9.AP.55.244; 9.AP.55.243; 9.AP.55.247; 9.AP.56.157; 9.AP.56.158; 9.AP.56.196; 9.AP.56.223; 9.AP.56.240; 9.AP.56.244; 9.AP.56.243; 9.AP.56.247; 9.AP.157.157; 9.AP.157.158; 9.AP.157.196; 9.AP.157.223; 9.AP.157.240; 9.AP.157.244; 9.AP.157.243; 9.AP.157.247; 9.AP.196.157; 9.AP.196.158; 9.AP.196.196; 9.AP.196.223; 9.AP.196.240; 9.AP.196.244; 9.AP.196.243; 9.AP.196.247; 9.AP.223.157; 9.AP.223.158; 9.AP.223.196; 9.AP.223.223; 9.AP.223.240; 9.AP.223.244; 9.AP.223.243; 9.AP.223.247; 9.AP.240.157; 9.AP.240.158; 9.AP.240.196; 9.AP.240.223; 9.AP.240.240; 9.AP.240.244; 9.AP.240.243; 9.AP.240.247; 9.AP.244.157; 9.AP.244.158; 9.AP.244.196; 9.AP.244.223; 9.AP.244.240; 9.AP.244.244; 9.AP.244.243; 9.AP.244.247; 9.AP.247.157; 9.AP.247.158; 9.AP.247.196; 9.AP.247.223; 9.AP.247.240; 9.AP.247.244; 9.AP.247.243; 9.AP.247.247;

Prodrugs of 9.AZ

9.AZ.4.157; 9.AZ.4.158; 9.AZ.4.196; 9.AZ.4.223; 9.AZ.4.240; 9.AZ.4.244; 9.AZ.4.243; 9.AZ.4.247; 9.AZ.5.157; 9.AZ.5.158; 9.AZ.5.196; 9.AZ.5.223; 9.AZ.5.240; 9.AZ.5.244; 9.AZ.5.243; 9.AZ.5.247; 9.AZ.7.157; 9.AZ.7.158; 9.AZ.7.196; 9.AZ.7.223; 9.AZ.7.240; 9.AZ.7.244; 9.AZ.7.243; 9.AZ.7.247; 9.AZ.15.157; 9.AZ.15.158; 9.AZ.15.196; 9.AZ.15.223; 9.AZ.15.240; 9.AZ.15.244; 9.AZ.15.243; 9.AZ.15.247; 9.AZ.16.157; 9.AZ.16.158; 9.AZ.16.196; 9.AZ.16.223; 9.AZ.16.240; 9.AZ.16.244; 9.AZ.16.243; 9.AZ.16.247; 9.AZ.18.157; 9.AZ.18.158; 9.AZ.18.196; 9.AZ.18.223; 9.AZ.18.240; 9.AZ.18.244; 9.AZ.18.243; 9.AZ.18.247; 9.AZ.26.157; 9.AZ.26.158; 9.AZ.26.196; 9.AZ.26.223; 9.AZ.26.240; 9.AZ.26.244; 9.AZ.26.243; 9.AZ.26.247; 9.AZ.27.157; 9.AZ.27.158; 9.AZ.27.196; 9.AZ.27.223; 9.AZ.27.240; 9.AZ.27.244; 9.AZ.27.243; 9.AZ.27.247; 9.AZ.29.157; 9.AZ.29.158; 9.AZ.29.196; 9.AZ.29.223; 9.AZ.29.240; 9.AZ.29.244; 9.AZ.29.243; 9.AZ.29.247; 9.AZ.54.157; 9.AZ.54.158; 9.AZ.54.196; 9.AZ.54.223; 9.AZ.54.240; 9.AZ.54.244; 9.AZ.54.243; 9.AZ.54.247; 9.AZ.55.157; 9.AZ.55.158; 9.AZ.55.196; 9.AZ.55.223; 9.AZ.55.240; 9.AZ.55.244; 9.AZ.55.243; 9.AZ.55.247; 9.AZ.56.157; 9.AZ.56.158; 9.AZ.56.196; 9.AZ.56.223; 9.AZ.56.240; 9.AZ.56.244; 9.AZ.56.243; 9.AZ.56.247; 9.AZ.157.157; 9.AZ.157.158; 9.AZ.157.196; 9.AZ.157.223;

9.AZ.157.240; 9.AZ.157.244; 9.AZ.157.243; 9.AZ.157.247; 9.AZ.196.157; 9.AZ.196.158; 9.AZ.196.196; 9.AZ.196.223; 9.AZ.196.240; 9.AZ.196.244; 9.AZ.196.243; 9.AZ.196.247; 9.AZ.223.157; 9.AZ.223.158; 9.AZ.223.196; 9.AZ.223.223; 9.AZ.223.240; 9.AZ.223.244; 9.AZ.223.243; 9.AZ.223.247; 9.AZ.240.157; 9.AZ.240.158; 9.AZ.240.196; 9.AZ.240.223; 9.AZ.240.240; 9.AZ.240.244; 9.AZ.240.243; 9.AZ.240.247; 9.AZ.244.157; 9.AZ.244.158; 9.AZ.244.196; 9.AZ.244.223; 9.AZ.244.240; 9.AZ.244.244; 9.AZ.244.243; 9.AZ.244.247; 9.AZ.247.157; 9.AZ.247.158; 9.AZ.247.196; 9.AZ.247.223; 9.AZ.247.240; 9.AZ.247.244; 9.AZ.247.243; 9.AZ.247.247;

Prodrugs of 9.BF

9.BF.4.157; 9.BF.4.158; 9.BF.4.196; 9.BF.4.223; 9.BF.4.240; 9.BF.4.244; 9.BF.4.243; 9.BF.4.247; 9.BF.5.157; 9.BF.5.158; 9.BF.5.196; 9.BF.5.223; 9.BF.5.240; 9.BF.5.244; 9.BF.5.243; 9.BF.5.247; 9.BF.7.157; 9.BF.7.158; 9.BF.7.196; 9.BF.7.223; 9.BF.7.240; 9.BF.7.244; 9.BF.7.243; 9.BF.7.247; 9.BF.15.157; 9.BF.15.158; 9.BF.15.196; 9.BF.15.223; 9.BF.15.240; 9.BF.15.244; 9.BF.15.243; 9.BF.15.247; 9.BF.16.157; 9.BF.16.158; 9.BF.16.196; 9.BF.16.223; 9.BF.16.240; 9.BF.16.244; 9.BF.16.243; 9.BF.16.247; 9.BF.18.157; 9.BF.18.158; 9.BF.18.196; 9.BF.18.223; 9.BF.18.240; 9.BF.18.244; 9.BF.18.243; 9.BF.18.247; 9.BF.26.157; 9.BF.26.158; 9.BF.26.196; 9.BF.26.223; 9.BF.26.240; 9.BF.26.244; 9.BF.26.243; 9.BF.26.247; 9.BF.27.157; 9.BF.27.158; 9.BF.27.196; 9.BF.27.223; 9.BF.27.240; 9.BF.27.244; 9.BF.27.243; 9.BF.27.247; 9.BF.29.157; 9.BF.29.158; 9.BF.29.196; 9.BF.29.223; 9.BF.29.240; 9.BF.29.244; 9.BF.29.243; 9.BF.29.247; 9.BF.54.157; 9.BF.54.158; 9.BF.54.196; 9.BF.54.223; 9.BF.54.240; 9.BF.54.244; 9.BF.54.243; 9.BF.54.247; 9.BF.55.157; 9.BF.55.158; 9.BF.55.196; 9.BF.55.223; 9.BF.55.240; 9.BF.55.244; 9.BF.55.243; 9.BF.55.247; 9.BF.56.157; 9.BF.56.158; 9.BF.56.196; 9.BF.56.223; 9.BF.56.240; 9.BF.56.244; 9.BF.56.243; 9.BF.56.247; 9.BF.157.157; 9.BF.157.158; 9.BF.157.196; 9.BF.157.223; 9.BF.157.240; 9.BF.157.244; 9.BF.157.243; 9.BF.157.247; 9.BF.196.157; 9.BF.196.158; 9.BF.196.196; 9.BF.196.223; 9.BF.196.240; 9.BF.196.244; 9.BF.196.243; 9.BF.196.247; 9.BF.223.157; 9.BF.223.158; 9.BF.223.196; 9.BF.223.223; 9.BF.223.240; 9.BF.223.244; 9.BF.223.243; 9.BF.223.247; 9.BF.240.157; 9.BF.240.158; 9.BF.240.196; 9.BF.240.223; 9.BF.240.240; 9.BF.240.244; 9.BF.240.243; 9.BF.240.247; 9.BF.244.157; 9.BF.244.158; 9.BF.244.196; 9.BF.244.223; 9.BF.244.240; 9.BF.244.244; 9.BF.244.243; 9.BF.244.247; 9.BF.247.157; 9.BF.247.158; 9.BF.247.196; 9.BF.247.223; 9.BF.247.240; 9.BF.247.244; 9.BF.247.243; 9.BF.247.247;

Prodrugs of 9.CI

9.CI.4.157; 9.CI.4.158; 9.CI.4.196; 9.CI.4.223; 9.CI.4.240; 9.CI.4.244; 9.CI.4.243; 9.CI.4.247; 9.CI.5.157; 9.CI.5.158; 9.CI.5.196; 9.CI.5.223; 9.CI.5.240; 9.CI.5.244; 9.CI.5.243; 9.CI.5.247; 9.CI.7.157; 9.CI.7.158; 9.CI.7.196; 9.CI.7.223; 9.CI.7.240; 9.CI.7.244; 9.CI.7.243; 9.CI.7.247; 9.CI.15.157; 9.CI.15.158; 9.CI.15.196; 9.CI.15.223; 9.CI.15.240; 9.CI.15.244; 9.CI.15.243; 9.CI.15.247; 9.CI.16.157; 9.CI.16.158; 9.CI.16.196; 9.CI.16.223; 9.CI.16.240; 9.CI.16.244; 9.CI.16.243; 9.CI.16.247; 9.CI.18.157; 9.CI.18.158; 9.CI.18.196; 9.CI.18.223; 9.CI.18.240; 9.CI.18.244; 9.CI.18.243; 9.CI.18.247; 9.CI.26.157; 9.CI.26.158; 9.CI.26.196; 9.CI.26.223; 9.CI.26.240; 9.CI.26.244; 9.CI.26.243; 9.CI.26.247; 9.CI.27.157; 9.CI.27.158; 9.CI.27.196; 9.CI.27.223; 9.CI.27.240; 9.CI.27.244; 9.CI.27.243; 9.CI.27.247; 9.CI.29.157; 9.CI.29.158; 9.CI.29.196; 9.CI.29.223; 9.CI.29.240; 9.CI.29.244; 9.CI.29.243; 9.CI.29.247; 9.CI.54.157; 9.CI.54.158; 9.CI.54.196; 9.CI.54.223; 9.CI.54.240; 9.CI.54.244; 9.CI.54.243; 9.CI.54.247; 9.CI.55.157; 9.CI.55.158; 9.CI.55.196; 9.CI.55.223;

9.CI.55.240; 9.CI.55.244; 9.CI.55.243; 9.CI.55.247; 9.CI.56.157; 9.CI.56.158; 9.CI.56.196; 9.CI.56.223; 9.CI.56.240; 9.CI.56.244; 9.CI.56.243; 9.CI.56.247; 9.CI.157.157; 9.CI.157.158; 9.CI.157.196; 9.CI.157.223; 9.CI.157.240; 9.CI.157.244; 9.CI.157.243; 9.CI.157.247; 9.CI.196.157; 9.CI.196.158; 9.CI.196.196; 9.CI.196.223; 9.CI.196.240; 9.CI.196.244; 9.CI.196.243; 9.CI.196.247; 9.CI.223.157; 9.CI.223.158; 9.CI.223.196; 9.CI.223.223; 9.CI.223.240; 9.CI.223.244; 9.CI.223.243; 9.CI.223.247; 9.CI.240.157; 9.CI.240.158; 9.CI.240.196; 9.CI.240.223; 9.CI.240.240; 9.CI.240.244; 9.CI.240.243; 9.CI.240.247; 9.CI.244.157; 9.CI.244.158; 9.CI.244.196; 9.CI.244.223; 9.CI.244.240; 9.CI.244.244; 9.CI.244.243; 9.CI.244.247; 9.CI.247.157; 9.CI.247.158; 9.CI.247.196; 9.CI.247.223; 9.CI.247.240; 9.CI.247.244; 9.CI.247.243; 9.CI.247.247;

Prodrugs of 9.CO

9.CO.4.157; 9.CO.4.158; 9.CO.4.196; 9.CO.4.223; 9.CO.4.240; 9.CO.4.244; 9.CO.4.243; 9.CO.4.247; 9.CO.5.157; 9.CO.5.158; 9.CO.5.196; 9.CO.5.223; 9.CO.5.240; 9.CO.5.244; 9.CO.5.243; 9.CO.5.247; 9.CO.7.157; 9.CO.7.158; 9.CO.7.196; 9.CO.7.223; 9.CO.7.240; 9.CO.7.244; 9.CO.7.243; 9.CO.7.247; 9.CO.15.157; 9.CO.15.158; 9.CO.15.196; 9.CO.15.223; 9.CO.15.240; 9.CO.15.244; 9.CO.15.243; 9.CO.15.247; 9.CO.16.157; 9.CO.16.158; 9.CO.16.196; 9.CO.16.223; 9.CO.16.240; 9.CO.16.244; 9.CO.16.243; 9.CO.16.247; 9.CO.18.157; 9.CO.18.158; 9.CO.18.196; 9.CO.18.223; 9.CO.18.240; 9.CO.18.244; 9.CO.18.243; 9.CO.18.247; 9.CO.26.157; 9.CO.26.158; 9.CO.26.196; 9.CO.26.223; 9.CO.26.240; 9.CO.26.244; 9.CO.26.243; 9.CO.26.247; 9.CO.27.157; 9.CO.27.158; 9.CO.27.196; 9.CO.27.223; 9.CO.27.240; 9.CO.27.244; 9.CO.27.243; 9.CO.27.247; 9.CO.29.157; 9.CO.29.158; 9.CO.29.196; 9.CO.29.223; 9.CO.29.240; 9.CO.29.244; 9.CO.29.243; 9.CO.29.247; 9.CO.54.157; 9.CO.54.158; 9.CO.54.196; 9.CO.54.223; 9.CO.54.240; 9.CO.54.244; 9.CO.54.243; 9.CO.54.247; 9.CO.55.157; 9.CO.55.158; 9.CO.55.196; 9.CO.55.223; 9.CO.55.240; 9.CO.55.244; 9.CO.55.243; 9.CO.55.247; 9.CO.56.157; 9.CO.56.158; 9.CO.56.196; 9.CO.56.223; 9.CO.56.240; 9.CO.56.244; 9.CO.56.243; 9.CO.56.247; 9.CO.157.157; 9.CO.157.158; 9.CO.157.196; 9.CO.157.223; 9.CO.157.240; 9.CO.157.244; 9.CO.157.243; 9.CO.157.247; 9.CO.196.157; 9.CO.196.158; 9.CO.196.196; 9.CO.196.223; 9.CO.196.240; 9.CO.196.244; 9.CO.196.243; 9.CO.196.247; 9.CO.223.157; 9.CO.223.158; 9.CO.223.196; 9.CO.223.223; 9.CO.223.240; 9.CO.223.244; 9.CO.223.243; 9.CO.223.247; 9.CO.240.157; 9.CO.240.158; 9.CO.240.196; 9.CO.240.223; 9.CO.240.240; 9.CO.240.244; 9.CO.240.243; 9.CO.240.247; 9.CO.244.157; 9.CO.244.158; 9.CO.244.196; 9.CO.244.223; 9.CO.244.240; 9.CO.244.244; 9.CO.244.243; 9.CO.244.247; 9.CO.247.157; 9.CO.247.158; 9.CO.247.196; 9.CO.247.223; 9.CO.247.240; 9.CO.247.244; 9.CO.247.243; 9.CO.247.247;

Prodrugs of 10.AH

10.AH.4.157; 10.AH.4.158; 10.AH.4.196; 10.AH.4.223; 10.AH.4.240; 10.AH.4.244; 10.AH.4.243; 10.AH.4.247; 10.AH.5.157; 10.AH.5.158; 10.AH.5.196; 10.AH.5.223; 10.AH.5.240; 10.AH.5.244; 10.AH.5.243; 10.AH.5.247; 10.AH.7.157; 10.AH.7.158; 10.AH.7.196; 10.AH.7.223; 10.AH.7.240; 10.AH.7.244; 10.AH.7.243; 10.AH.7.247; 10.AH.15.157; 10.AH.15.158; 10.AH.15.196; 10.AH.15.223; 10.AH.15.240; 10.AH.15.244; 10.AH.15.243; 10.AH.15.247; 10.AH.16.157; 10.AH.16.158; 10.AH.16.196; 10.AH.16.223; 10.AH.16.240; 10.AH.16.244; 10.AH.16.243; 10.AH.16.247; 10.AH.18.157; 10.AH.18.158; 10.AH.18.196; 10.AH.18.223; 10.AH.18.240; 10.AH.18.244; 10.AH.18.243; 10.AH.18.247; 10.AH.26.157; 10.AH.26.158; 10.AH.26.196; 10.AH.26.223; 10.AH.26.240; 10.AH.26.244; 10.AH.26.243; 10.AH.26.247; 10.AH.27.157; 10.AH.27.158; 10.AH.27.196; 10.AH.27.223;

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Prodrugs of 10.AJ

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Prodrugs of 10.AN

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Prodrugs of 10.AP

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Prodrugs of 10.AZ

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Prodrugs of 10.BF

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Prodrugs of 10.CI

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Prodrugs of 10.CO

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Prodrugs of 11.AH

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Prodrugs of 11.AJ

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Prodrugs of 11.AN

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Prodrugs of 11.AP

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Prodrugs of 11.AZ

11.AZ.4.157; 11.AZ.4.158; 11.AZ.4.196; 11.AZ.4.223; 11.AZ.4.240; 11.AZ.4.244; 11.AZ.4.243; 11.AZ.4.247; 11.AZ.5.157; 11.AZ.5.158; 11.AZ.5.196; 11.AZ.5.223; 11.AZ.5.240; 11.AZ.5.244; 11.AZ.5.243; 11.AZ.5.247; 11.AZ.7.157; 11.AZ.7.158; 11.AZ.7.196; 11.AZ.7.223; 11.AZ.7.240; 11.AZ.7.244; 11.AZ.7.243; 11.AZ.7.247; 11.AZ.15.157; 11.AZ.15.158; 11.AZ.15.196; 11.AZ.15.223; 11.AZ.15.240; 11.AZ.15.244; 11.AZ.15.243; 11.AZ.15.247; 11.AZ.16.157; 11.AZ.16.158; 11.AZ.16.196; 11.AZ.16.223; 11.AZ.16.240; 11.AZ.16.244; 11.AZ.16.243; 11.AZ.16.247; 11.AZ.18.157; 11.AZ.18.158; 11.AZ.18.196; 11.AZ.18.223; 11.AZ.18.240; 11.AZ.18.244; 11.AZ.18.243; 11.AZ.18.247; 11.AZ.26.157; 11.AZ.26.158; 11.AZ.26.196; 11.AZ.26.223; 11.AZ.26.240; 11.AZ.26.244; 11.AZ.26.243; 11.AZ.26.247; 11.AZ.27.157; 11.AZ.27.158; 11.AZ.27.196; 11.AZ.27.223; 11.AZ.27.240; 11.AZ.27.244; 11.AZ.27.243; 11.AZ.27.247; 11.AZ.29.157; 11.AZ.29.158; 11.AZ.29.196; 11.AZ.29.223; 11.AZ.29.240; 11.AZ.29.244; 11.AZ.29.243; 11.AZ.29.247;

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Prodrugs of 11.BF

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Prodrugs of 11.CI

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Prodrugs of 11.CO

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Prodrugs of 12.AH

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Prodrugs of 12.AJ

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Prodrugs of 12.AN

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Prodrugs of 12.AP

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Prodrugs of 12.AZ

12.AZ.4.157; 12.AZ.4.158; 12.AZ.4.196; 12.AZ.4.223; 12.AZ.4.240; 12.AZ.4.244; 12.AZ.4.243; 12.AZ.4.247; 12.AZ.5.157; 12.AZ.5.158; 12.AZ.5.196; 12.AZ.5.223; 12.AZ.5.240; 12.AZ.5.244; 12.AZ.5.243; 12.AZ.5.247; 12.AZ.7.157; 12.AZ.7.158; 12.AZ.7.196; 12.AZ.7.223; 12.AZ.7.240; 12.AZ.7.244; 12.AZ.7.243; 12.AZ.7.247; 12.AZ.15.157; 12.AZ.15.158; 12.AZ.15.196; 12.AZ.15.223; 12.AZ.15.240; 12.AZ.15.244; 12.AZ.15.243; 12.AZ.15.247; 12.AZ.16.157; 12.AZ.16.158; 12.AZ.16.196; 12.AZ.16.223; 12.AZ.16.240; 12.AZ.16.244; 12.AZ.16.243; 12.AZ.16.247; 12.AZ.18.157; 12.AZ.18.158; 12.AZ.18.196; 12.AZ.18.223; 12.AZ.18.240; 12.AZ.18.244; 12.AZ.18.243; 12.AZ.18.247; 12.AZ.26.157; 12.AZ.26.158; 12.AZ.26.196; 12.AZ.26.223; 12.AZ.26.240; 12.AZ.26.244; 12.AZ.26.243; 12.AZ.26.247; 12.AZ.27.157; 12.AZ.27.158; 12.AZ.27.196; 12.AZ.27.223; 12.AZ.27.240; 12.AZ.27.244; 12.AZ.27.243; 12.AZ.27.247; 12.AZ.29.157; 12.AZ.29.158; 12.AZ.29.196; 12.AZ.29.223; 12.AZ.29.240; 12.AZ.29.244; 12.AZ.29.243; 12.AZ.29.247; 12.AZ.54.157; 12.AZ.54.158; 12.AZ.54.196; 12.AZ.54.223; 12.AZ.54.240; 12.AZ.54.244; 12.AZ.54.243; 12.AZ.54.247; 12.AZ.55.157; 12.AZ.55.158; 12.AZ.55.196; 12.AZ.55.223; 12.AZ.55.240; 12.AZ.55.244; 12.AZ.55.243; 12.AZ.55.247; 12.AZ.56.157; 12.AZ.56.158; 12.AZ.56.196; 12.AZ.56.223; 12.AZ.56.240; 12.AZ.56.244; 12.AZ.56.243; 12.AZ.56.247; 12.AZ.157.157; 12.AZ.157.158; 12.AZ.157.196; 12.AZ.157.223; 12.AZ.157.240; 12.AZ.157.244; 12.AZ.157.243; 12.AZ.157.247; 12.AZ.196.157; 12.AZ.196.158; 12.AZ.196.196; 12.AZ.196.223; 12.AZ.196.240; 12.AZ.196.244; 12.AZ.196.243; 12.AZ.196.247; 12.AZ.223.157; 12.AZ.223.158; 12.AZ.223.196; 12.AZ.223.223; 12.AZ.223.240; 12.AZ.223.244; 12.AZ.223.243; 12.AZ.223.247; 12.AZ.240.157; 12.AZ.240.158; 12.AZ.240.196; 12.AZ.240.223; 12.AZ.240.240; 12.AZ.240.244; 12.AZ.240.243; 12.AZ.240.247; 12.AZ.244.157; 12.AZ.244.158; 12.AZ.244.196; 12.AZ.244.223; 12.AZ.244.240; 12.AZ.244.244; 12.AZ.244.243; 12.AZ.244.247; 12.AZ.247.157; 12.AZ.247.158; 12.AZ.247.196; 12.AZ.247.223; 12.AZ.247.240; 12.AZ.247.244; 12.AZ.247.243; 12.AZ.247.247;

Prodrugs of 12.BF

12.BF.4.157; 12.BF.4.158; 12.BF.4.196; 12.BF.4.223; 12.BF.4.240; 12.BF.4.244; 12.BF.4.243; 12.BF.4.247; 12.BF.5.157; 12.BF.5.158; 12.BF.5.196; 12.BF.5.223;

12.BF.5.240; 12.BF.5.244; 12.BF.5.243; 12.BF.5.247; 12.BF.7.157; 12.BF.7.158; 12.BF.7.196; 12.BF.7.223; 12.BF.7.240; 12.BF.7.244; 12.BF.7.243; 12.BF.7.247; 12.BF.15.157; 12.BF.15.158; 12.BF.15.196; 12.BF.15.223; 12.BF.15.240; 12.BF.15.244; 12.BF.15.243; 12.BF.15.247; 12.BF.16.157; 12.BF.16.158; 12.BF.16.196; 12.BF.16.223; 12.BF.16.240; 12.BF.16.244; 12.BF.16.243; 12.BF.16.247; 12.BF.18.157; 12.BF.18.158; 12.BF.18.196; 12.BF.18.223; 12.BF.18.240; 12.BF.18.244; 12.BF.18.243; 12.BF.18.247; 12.BF.26.157; 12.BF.26.158; 12.BF.26.196; 12.BF.26.223; 12.BF.26.240; 12.BF.26.244; 12.BF.26.243; 12.BF.26.247; 12.BF.27.157; 12.BF.27.158; 12.BF.27.196; 12.BF.27.223; 12.BF.27.240; 12.BF.27.244; 12.BF.27.243; 12.BF.27.247; 12.BF.29.157; 12.BF.29.158; 12.BF.29.196; 12.BF.29.223; 12.BF.29.240; 12.BF.29.244; 12.BF.29.243; 12.BF.29.247; 12.BF.54.157; 12.BF.54.158; 12.BF.54.196; 12.BF.54.223; 12.BF.54.240; 12.BF.54.244; 12.BF.54.243; 12.BF.54.247; 12.BF.55.157; 12.BF.55.158; 12.BF.55.196; 12.BF.55.223; 12.BF.55.240; 12.BF.55.244; 12.BF.55.243; 12.BF.55.247; 12.BF.56.157; 12.BF.56.158; 12.BF.56.196; 12.BF.56.223; 12.BF.56.240; 12.BF.56.244; 12.BF.56.243; 12.BF.56.247; 12.BF.157.157; 12.BF.157.158; 12.BF.157.196; 12.BF.157.223; 12.BF.157.240; 12.BF.157.244; 12.BF.157.243; 12.BF.157.247; 12.BF.196.157; 12.BF.196.158; 12.BF.196.196; 12.BF.196.223; 12.BF.196.240; 12.BF.196.244; 12.BF.196.243; 12.BF.196.247; 12.BF.223.157; 12.BF.223.158; 12.BF.223.196; 12.BF.223.223; 12.BF.223.240; 12.BF.223.244; 12.BF.223.243; 12.BF.223.247; 12.BF.240.157; 12.BF.240.158; 12.BF.240.196; 12.BF.240.223; 12.BF.240.240; 12.BF.240.244; 12.BF.240.243; 12.BF.240.247; 12.BF.244.157; 12.BF.244.158; 12.BF.244.196; 12.BF.244.223; 12.BF.244.240; 12.BF.244.244; 12.BF.244.243; 12.BF.244.247; 12.BF.247.157; 12.BF.247.158; 12.BF.247.196; 12.BF.247.223; 12.BF.247.240; 12.BF.247.244; 12.BF.247.243; 12.BF.247.247;

<u>Prodrugs of 12.CI</u>

12.CI.4.157; 12.CI.4.158; 12.CI.4.196; 12.CI.4.223; 12.CI.4.240; 12.CI.4.244; 12.CI.4.243; 12.CI.4.247; 12.CI.5.157; 12.CI.5.158; 12.CI.5.196; 12.CI.5.223; 12.CI.5.240; 12.CI.5.244; 12.CI.5.243; 12.CI.5.247; 12.CI.7.157; 12.CI.7.158; 12.CI.7.196; 12.CI.7.223; 12.CI.7.240; 12.CI.7.244; 12.CI.7.243; 12.CI.7.247; 12.CI.15.157; 12.CI.15.158; 12.CI.15.196; 12.CI.15.223; 12.CI.15.240; 12.CI.15.244; 12.CI.15.243; 12.CI.15.247; 12.CI.16.157; 12.CI.16.158; 12.CI.16.196; 12.CI.16.223; 12.CI.16.240; 12.CI.16.244; 12.CI.16.243; 12.CI.16.247; 12.CI.18.157; 12.CI.18.158; 12.CI.18.196; 12.CI.18.223; 12.CI.18.240; 12.CI.18.244; 12.CI.18.243; 12.CI.18.247; 12.CI.26.157; 12.CI.26.158; 12.CI.26.196; 12.CI.26.223; 12.CI.26.240; 12.CI.26.244; 12.CI.26.243; 12.CI.26.247; 12.CI.27.157; 12.CI.27.158; 12.CI.27.196; 12.CI.27.223; 12.CI.27.240; 12.CI.27.244; 12.CI.27.243; 12.CI.27.247; 12.CI.29.157; 12.CI.29.158; 12.CI.29.196; 12.CI.29.223; 12.CI.29.240; 12.CI.29.244; 12.CI.29.243; 12.CI.29.247; 12.CI.54.157; 12.CI.54.158; 12.CI.54.196; 12.CI.54.223; 12.CI.54.240; 12.CI.54.244; 12.CI.54.243; 12.CI.54.247; 12.CI.55.157; 12.CI.55.158; 12.CI.55.196; 12.CI.55.223; 12.CI.55.240; 12.CI.55.244; 12.CI.55.243; 12.CI.55.247; 12.CI.56.157; 12.CI.56.158; 12.CI.56.196; 12.CI.56.223; 12.CI.56.240; 12.CI.56.244; 12.CI.56.243; 12.CI.56.247; 12.CI.157.157; 12.CI.157.158; 12.CI.157.196; 12.CI.157.223; 12.CI.157.240; 12.CI.157.244; 12.CI.157.243; 12.CI.157.247; 12.CI.196.157; 12.CI.196.158; 12.CI.196.196; 12.CI.196.223; 12.CI.196.240; 12.CI.196.244; 12.CI.196.243; 12.CI.196.247; 12.CI.223.157; 12.CI.223.158; 12.CI.223.196; 12.CI.223.223; 12.CI.223.240; 12.CI.223.244; 12.CI.223.243; 12.CI.223.247; 12.CI.240.157; 12.CI.240.158; 12.CI.240.196; 12.CI.240.223; 12.CI.240.240; 12.CI.240.244; 12.CI.240.243; 12.CI.240.247; 12.CI.244.157; 12.CI.244.158; 12.CI.244.196; 12.CI.244.223; 12.CI.244.240; 12.CI.244.244;

12.CI.244.243; 12.CI.244.247; 12.CI.247.157; 12.CI.247.158; 12.CI.247.196; 12.CI.247.223; 12.CI.247.240; 12.CI.247.244; 12.CI.247.243; 12.CI.247.247;

Prodrugs of 12.CO

12.CO.4.157; 12.CO.4.158; 12.CO.4.196; 12.CO.4.223; 12.CO.4.240; 12.CO.4.244; 12.CO.4.243; 12.CO.4.247; 12.CO.5.157; 12.CO.5.158; 12.CO.5.196; 12.CO.5.223; 12.CO.5.240; 12.CO.5.244; 12.CO.5.243; 12.CO.5.247; 12.CO.7.157; 12.CO.7.158; 12.CO.7.196; 12.CO.7.223; 12.CO.7.240; 12.CO.7.244; 12.CO.7.243; 12.CO.7.247; 12.CO.15.157; 12.CO.15.158; 12.CO.15.196; 12.CO.15.223; 12.CO.15.240; 12.CO.15.244; 12.CO.15.243; 12.CO.15.247; 12.CO.16.157; 12.CO.16.158; 12.CO.16.196; 12.CO.16.223; 12.CO.16.240; 12.CO.16.244; 12.CO.16.243; 12.CO.16.247; 12.CO.18.157; 12.CO.18.158; 12.CO.18.196; 12.CO.18.223; 12.CO.18.240; 12.CO.18.244; 12.CO.18.243; 12.CO.18.247; 12.CO.26.157; 12.CO.26.158; 12.CO.26.196; 12.CO.26.223; 12.CO.26.240; 12.CO.26.244; 12.CO.26.243; 12.CO.26.247; 12.CO.27.157; 12.CO.27.158; 12.CO.27.196; 12.CO.27.223; 12.CO.27.240; 12.CO.27.244; 12.CO.27.243; 12.CO.27.247; 12.CO.29.157; 12.CO.29.158; 12.CO.29.196; 12.CO.29.223; 12.CO.29.240; 12.CO.29.244; 12.CO.29.243; 12.CO.29.247; 12.CO.54.157; 12.CO.54.158; 12.CO.54.196; 12.CO.54.223; 12.CO.54.240; 12.CO.54.244; 12.CO.54.243; 12.CO.54.247; 12.CO.55.157; 12.CO.55.158; 12.CO.55.196; 12.CO.55.223; 12.CO.55.240; 12.CO.55.244; 12.CO.55.243; 12.CO.55.247; 12.CO.56.157; 12.CO.56.158; 12.CO.56.196; 12.CO.56.223; 12.CO.56.240; 12.CO.56.244; 12.CO.56.243; 12.CO.56.247; 12.CO.157.157; 12.CO.157.158; 12.CO.157.196; 12.CO.157.223; 12.CO.157.240; 12.CO.157.244; 12.CO.157.243; 12.CO.157.247; 12.CO.196.157; 12.CO.196.158; 12.CO.196.196; 12.CO.196.223; 12.CO.196.240; 12.CO.196.244; 12.CO.196.243; 12.CO.196.247; 12.CO.223.157; 12.CO.223.158; 12.CO.223.196; 12.CO.223.223; 12.CO.223.240; 12.CO.223.244; 12.CO.223.243; 12.CO.223.247; 12.CO.240.157; 12.CO.240.158; 12.CO.240.196; 12.CO.240.223; 12.CO.240.240; 12.CO.240.244; 12.CO.240.243; 12.CO.240.247; 12.CO.244.157; 12.CO.244.158; 12.CO.244.196; 12.CO.244.223; 12.CO.244.240; 12.CO.244.244; 12.CO.244.243; 12.CO.244.247; 12.CO.247.157; 12.CO.247.158; 12.CO.247.196; 12.CO.247.223; 12.CO.247.240; 12.CO.247.244; 12.CO.247.243; 12.CO.247.247.

Prodrugs of 13.B

13.B.228.228; 13.B.228.229; 13.B.228.230; 13.B.228.231; 13.B.228.236; 13.B.228.237; 13.B.228.238; 13.B.228.239; 13.B.228.154; 13.B.228.157; 13.B.228.166; 13.B.228.169; 13.B.228.172; 13.B.228.175; 13.B.228.240; 13.B.228.244; 13.B.229.228; 13.B.229.229; 13.B.229.230; 13.B.229.231; 13.B.229.236; 13.B.229.237; 13.B.229.238; 13.B.229.239; 13.B.229.154; 13.B.229.157; 13.B.229.166; 13.B.229.169; 13.B.229.172; 13.B.229.175; 13.B.229.240; 13.B.229.244; 13.B.230.228; 13.B.230.229; 13.B.230.230; 13.B.230.231; 13.B.230.236; 13.B.230.237; 13.B.230.238; 13.B.230.239; 13.B.230.154; 13.B.230.157; 13.B.230.166; 13.B.230.169; 13.B.230.172; 13.B.230.175; 13.B.230.240; 13.B.230.244; 13.B.231.228; 13.B.231.229; 13.B.231.230; 13.B.231.231; 13.B.231.236; 13.B.231.237; 13.B.231.238; 13.B.231.239; 13.B.231.154; 13.B.231.157; 13.B.231.166; 13.B.231.169; 13.B.231.172; 13.B.231.175; 13.B.231.240; 13.B.231.244; 13.B.236.228; 13.B.236.229; 13.B.236.230; 13.B.236.231; 13.B.236.236; 13.B.236.237; 13.B.236.238; 13.B.236.239; 13.B.236.154; 13.B.236.157; 13.B.236.166; 13.B.236.169; 13.B.236.172; 13.B.236.175; 13.B.236.240; 13.B.236.244; 13.B.237.228; 13.B.237.229; 13.B.237.230; 13.B.237.231; 13.B.237.236; 13.B.237.237; 13.B.237.238; 13.B.237.239; 13.B.237.154; 13.B.237.157; 13.B.237.166; 13.B.237.169; 13.B.237.172; 13.B.237.175; 13.B.237.240; 13.B.237.244; 13.B.238.228; 13.B.238.229; 13.B.238.230; 13.B.238.231; 13.B.238.236; 13.B.238.237; 13.B.238.238; 13.B.238.239; 13.B.238.154; 13.B.238.157; 13.B.238.166; 13.B.238.169; 13.B.238.172; 13.B.238.175; 13.B.238.240; 13.B.238.244; 13.B.239.228; 13.B.239.229; 13.B.239.230; 13.B.239.231; 13.B.239.236; 13.B.239.237; 13.B.239.238; 13.B.239.239; 13.B.239.154; 13.B.239.157; 13.B.239.166; 13.B.239.169; 13.B.239.172; 13.B.239.175; 13.B.239.240; 13.B.239.244; 13.B.154.228; 13.B.154.229; 13.B.154.230; 13.B.154.231; 13.B.154.236; 13.B.154.237; 13.B.154.238; 13.B.154.239; 13.B.154.154; 13.B.154.157; 13.B.154.166; 13.B.154.169; 13.B.154.172; 13.B.154.175; 13.B.154.240; 13.B.154.244; 13.B.157.228; 13.B.157.229; 13.B.157.230; 13.B.157.231; 13.B.157.236; 13.B.157.237; 13.B.157.238; 13.B.157.239; 13.B.157.154; 13.B.157.157; 13.B.157.166; 13.B.157.169; 13.B.157.172; 13.B.157.175; 13.B.157.240; 13.B.157.244; 13.B.166.228; 13.B.166.229; 13.B.166.230; 13.B.166.231; 13.B.166.236; 13.B.166.237; 13.B.166.238; 13.B.166.239; 13.B.166.154; 13.B.166.157; 13.B.166.166; 13.B.166.169; 13.B.166.172; 13.B.166.175; 13.B.166.240; 13.B.166.244; 13.B.169.228; 13.B.169.229; 13.B.169.230; 13.B.169.231; 13.B.169.236; 13.B.169.237; 13.B.169.238; 13.B.169.239; 13.B.169.154; 13.B.169.157; 13.B.169.166; 13.B.169.169; 13.B.169.172; 13.B.169.175; 13.B.169.240; 13.B.169.244; 13.B.172.228; 13.B.172.229; 13.B.172.230; 13.B.172.231; 13.B.172.236; 13.B.172.237; 13.B.172.238; 13.B.172.239; 13.B.172.154; 13.B.172.157; 13.B.172.166; 13.B.172.169; 13.B.172.172; 13.B.172.175; 13.B.172.240; 13.B.172.244; 13.B.175.228; 13.B.175.229; 13.B.175.230; 13.B.175.231; 13.B.175.236; 13.B.175.237; 13.B.175.238; 13.B.175.239; 13.B.175.154; 13.B.175.157; 13.B.175.166; 13.B.175.169; 13.B.175.172; 13.B.175.175; 13.B.175.240; 13.B.175.244; 13.B.240.228; 13.B.240.229; 13.B.240.230; 13.B.240.231; 13.B.240.236; 13.B.240.237; 13.B.240.238; 13.B.240.239; 13.B.240.154; 13.B.240.157; 13.B.240.166; 13.B.240.169; 13.B.240.172; 13.B.240.175; 13.B.240.240; 13.B.240.244; 13.B.244.228; 13.B.244.229; 13.B.244.230; 13.B.244.231; 13.B.244.236; 13.B.244.237; 13.B.244.238; 13.B.244.239; 13.B.244.154; 13.B.244.157; 13.B.244.166; 13.B.244.169; 13.B.244.172; 13.B.244.175; 13.B.244.240; 13.B.244.244;

Prodrugs of 13.D

13.D.228.228; 13.D.228.229; 13.D.228.230; 13.D.228.231; 13.D.228.236; 13.D.228.237; 13.D.228.238; 13.D.228.239; 13.D.228.154; 13.D.228.157; 13.D.228.166; 13.D.228.169; 13.D.228.172; 13.D.228.175; 13.D.228.240; 13.D.228.244; 13.D.229.228; 13.D.229.229; 13.D.229.230; 13.D.229.231; 13.D.229.236; 13.D.229.237; 13.D.229.238; 13.D.229.239; 13.D.229.154; 13.D.229.157; 13.D.229.166; 13.D.229.169; 13.D.229.172; 13.D.229.175; 13.D.229.240; 13.D.229.244; 13.D.230.228; 13.D.230.229; 13.D.230.230; 13.D.230.231; 13.D.230.236; 13.D.230.237; 13.D.230.238; 13.D.230.239; 13.D.230.154; 13.D.230.157; 13.D.230.166; 13.D.230.169; 13.D.230.172; 13.D.230.175; 13.D.230.240; 13.D.230.244; 13.D.231.228; 13.D.231.229; 13.D.231.230; 13.D.231.231; 13.D.231.236; 13.D.231.237; 13.D.231.238; 13.D.231.239; 13.D.231.154; 13.D.231.157; 13.D.231.166; 13.D.231.169; 13.D.231.172; 13.D.231.175; 13.D.231.240; 13.D.231.244; 13.D.236.228; 13.D.236.229; 13.D.236.230; 13.D.236.231; 13.D.236.236; 13.D.236.237; 13.D.236.238; 13.D.236.239; 13.D.236.154; 13.D.236.157; 13.D.236.166; 13.D.236.169; 13.D.236.172; 13.D.236.175; 13.D.236.240; 13.D.236.244; 13.D.237.228; 13.D.237.229; 13.D.237.230; 13.D.237.231; 13.D.237.236; 13.D.237.237; 13.D.237.238; 13.D.237.239; 13.D.237.154; 13.D.237.157; 13.D.237.166; 13.D.237.169; 13.D.237.172; 13.D.237.175; 13.D.237.240; 13.D.237.244; 13.D.238.228; 13.D.238.229; 13.D.238.230; 13.D.238.231; 13.D.238.236; 13.D.238.237; 13.D.238.238; 13.D.238.239; 13.D.238.154; 13.D.238.157; 13.D.238.166; 13.D.238.169; 13.D.238.172; 13.D.238.175; 13.D.238.240; 13.D.238.244; 13.D.239.228; 13.D.239.229; 13.D.239.230; 13.D.239.231; 13.D.239.236; 13.D.239.237; 13.D.239.238; 13.D.239.239; 13.D.239.154; 13.D.239.157; 13.D.239.166; 13.D.239.169; 13.D.239.172; 13.D.239.175; 13.D.239.240; 13.D.239.244; 13.D.154.228; 13.D.154.229; 13.D.154.230; 13.D.154.231; 13.D.154.236; 13.D.154.237; 13.D.154.238; 13.D.154.239; 13.D.154.154; 13.D.154.157; 13.D.154.166; 13.D.154.169; 13.D.154.172; 13.D.154.175; 13.D.154.240; 13.D.154.244; 13.D.157.228; 13.D.157.229; 13.D.157.230; 13.D.157.231; 13.D.157.236; 13.D.157.237; 13.D.157.238; 13.D.157.239; 13.D.157.154; 13.D.157.157; 13.D.157.166; 13.D.157.169; 13.D.157.172; 13.D.157.175; 13.D.157.240; 13.D.157.244; 13.D.166.228; 13.D.166.229; 13.D.166.230; 13.D.166.231; 13.D.166.236; 13.D.166.237; 13.D.166.238; 13.D.166.239; 13.D.166.154; 13.D.166.157; 13.D.166.166; 13.D.166.169; 13.D.166.172; 13.D.166.175; 13.D.166.240; 13.D.166.244; 13.D.169.228; 13.D.169.229; 13.D.169.230; 13.D.169.231; 13.D.169.236; 13.D.169.237; 13.D.169.238; 13.D.169.239; 13.D.169.154; 13.D.169.157; 13.D.169.166; 13.D.169.169; 13.D.169.172; 13.D.169.175; 13.D.169.240; 13.D.169.244; 13.D.172.228; 13.D.172.229; 13.D.172.230; 13.D.172.231; 13.D.172.236; 13.D.172.237; 13.D.172.238; 13.D.172.239; 13.D.172.154; 13.D.172.157; 13.D.172.166; 13.D.172.169; 13.D.172.172; 13.D.172.175; 13.D.172.240; 13.D.172.244; 13.D.175.228; 13.D.175.229; 13.D.175.230; 13.D.175.231; 13.D.175.236; 13.D.175.237; 13.D.175.238; 13.D.175.239; 13.D.175.154; 13.D.175.157; 13.D.175.166; 13.D.175.169; 13.D.175.172; 13.D.175.175; 13.D.175.240; 13.D.175.244; 13.D.240.228; 13.D.240.229; 13.D.240.230; 13.D.240.231; 13.D.240.236; 13.D.240.237; 13.D.240.238; 13.D.240.239; 13.D.240.154; 13.D.240.157; 13.D.240.166; 13.D.240.169; 13.D.240.172; 13.D.240.175; 13.D.240.240; 13.D.240.244; 13.D.244.228; 13.D.244.229; 13.D.244.230; 13.D.244.231; 13.D.244.236; 13.D.244.237; 13.D.244.238; 13.D.244.239; 13.D.244.154; 13.D.244.157; 13.D.244.166; 13.D.244.169; 13.D.244.172; 13.D.244.175; 13.D.244.240; 13.D.244.244;

Prodrugs of 13.E

13.E.228.228; 13.E.228.229; 13.E.228.230; 13.E.228.231; 13.E.228.236; 13.E.228.237; 13.E.228.238; 13.E.228.239; 13.E.228.154; 13.E.228.157; 13.E.228.166; 13.E.228.169; 13.E.228.172; 13.E.228.175; 13.E.228.240; 13.E.228.244; 13.E.229.228; 13.E.229.229; 13.E.229.230; 13.E.229.231; 13.E.229.236; 13.E.229.237; 13.E.229.238; 13.E.229.239; 13.E.229.154; 13.E.229.157; 13.E.229.166; 13.E.229.169; 13.E.229.172; 13.E.229.175; 13.E.229.240; 13.E.229.244; 13.E.230.228; 13.E.230.229; 13.E.230.230; 13.E.230.231; 13.E.230.236; 13.E.230.237; 13.E.230.238; 13.E.230.239; 13.E.230.154; 13.E.230.157; 13.E.230.166; 13.E.230.169; 13.E.230.172; 13.E.230.175; 13.E.230.240; 13.E.230.244; 13.E.231.228; 13.E.231.229; 13.E.231.230; 13.E.231.231; 13.E.231.236; 13.E.231.237; 13.E.231.238; 13.E.231.239; 13.E.231.154; 13.E.231.157; 13.E.231.166; 13.E.231.169; 13.E.231.172; 13.E.231.175; 13.E.231.240; 13.E.231.244; 13.E.236.228; 13.E.236.229; 13.E.236.230; 13.E.236.231; 13.E.236.236; 13.E.236.237; 13.E.236.238; 13.E.236.239; 13.E.236.154; 13.E.236.157; 13.E.236.166; 13.E.236.169; 13.E.236.172; 13.E.236.175; 13.E.236.240; 13.E.236.244; 13.E.237.228; 13.E.237.229; 13.E.237.230; 13.E.237.231; 13.E.237.236; 13.E.237.237; 13.E.237.238; 13.E.237.239; 13.E.237.154; 13.E.237.157; 13.E.237.166; 13.E.237.169; 13.E.237.172; 13.E.237.175; 13.E.237.240; 13.E.237.244; 13.E.238.228; 13.E.238.229; 13.E.238.230; 13.E.238.231; 13.E.238.236; 13.E.238.237; 13.E.238.238; 13.E.238.239; 13.E.238.154; 13.E.238.157; 13.E.238.166; 13.E.238.169; 13.E.238.172; 13.E.238.175; 13.E.238.240; 13.E.238.244; 13.E.239.228; 13.E.239.229; 13.E.239.230; 13.E.239.231; 13.E.239.236; 13.E.239.237; 13.E.239.238; 13.E.239.239; 13.E.239.154; 13.E.239.157; 13.E.239.166; 13.E.239.169; 13.E.239.172; 13.E.239.175; 13.E.239.240; 13.E.239.244; 13.E.154.228; 13.E.154.229; 13.E.154.230; 13.E.154.231; 13.E.154.236; 13.E.154.237; 13.E.154.238; 13.E.154.239; 13.E.154.154; 13.E.154.157; 13.E.154.166; 13.E.154.169; 13.E.154.172; 13.E.154.175; 13.E.154.240; 13.E.154.244; 13.E.157.228; 13.E.157.229; 13.E.157.230; 13.E.157.231; 13.E.157.236; 13.E.157.237; 13.E.157.238; 13.E.157.239; 13.E.157.154; 13.E.157.157; 13.E.157.166; 13.E.157.169; 13.E.157.172; 13.E.157.175; 13.E.157.240; 13.E.157.244; 13.E.166.228; 13.E.166.229; 13.E.166.230; 13.E.166.231; 13.E.166.236; 13.E.166.237; 13.E.166.238; 13.E.166.239; 13.E.166.154; 13.E.166.157; 13.E.166.166; 13.E.166.169; 13.E.166.172; 13.E.166.175; 13.E.166.240; 13.E.166.244; 13.E.169.228; 13.E.169.229; 13.E.169.230; 13.E.169.231; 13.E.169.236; 13.E.169.237; 13.E.169.238; 13.E.169.239; 13.E.169.154; 13.E.169.157; 13.E.169.166; 13.E.169.169; 13.E.169.172; 13.E.169.175; 13.E.169.240; 13.E.169.244; 13.E.172.228; 13.E.172.229; 13.E.172.230; 13.E.172.231; 13.E.172.236; 13.E.172.237; 13.E.172.238; 13.E.172.239; 13.E.172.154; 13.E.172.157; 13.E.172.166; 13.E.172.169; 13.E.172.172; 13.E.172.175; 13.E.172.240; 13.E.172.244; 13.E.175.228; 13.E.175.229; 13.E.175.230; 13.E.175.231; 13.E.175.236; 13.E.175.237; 13.E.175.238; 13.E.175.239; 13.E.175.154; 13.E.175.157; 13.E.175.166; 13.E.175.169; 13.E.175.172; 13.E.175.175; 13.E.175.240; 13.E.175.244; 13.E.240.228; 13.E.240.229; 13.E.240.230; 13.E.240.231; 13.E.240.236; 13.E.240.237; 13.E.240.238; 13.E.240.239; 13.E.240.154; 13.E.240.157; 13.E.240.166; 13.E.240.169; 13.E.240.172; 13.E.240.175; 13.E.240.240; 13.E.240.244; 13.E.244.228; 13.E.244.229; 13.E.244.230; 13.E.244.231; 13.E.244.236; 13.E.244.237; 13.E.244.238; 13.E.244.239; 13.E.244.154; 13.E.244.157; 13.E.244.166; 13.E.244.169; 13.E.244.172; 13.E.244.175; 13.E.244.240; 13.E.244.244;

Prodrugs of 13.G

13.G.228.228; 13.G.228.229; 13.G.228.230; 13.G.228.231; 13.G.228.236; 13.G.228.237; 13.G.228.238; 13.G.228.239; 13.G.228.154; 13.G.228.157; 13.G.228.166; 13.G.228.169; 13.G.228.172; 13.G.228.175; 13.G.228.240; 13.G.228.244; 13.G.229.228; 13.G.229.229; 13.G.229.230; 13.G.229.231; 13.G.229.236; 13.G.229.237; 13.G.229.238; 13.G.229.239; 13.G.229.154; 13.G.229.157; 13.G.229.166; 13.G.229.169; 13.G.229.172; 13.G.229.175; 13.G.229.240; 13.G.229.244; 13.G.230.228; 13.G.230.229; 13.G.230.230; 13.G.230.231; 13.G.230.236; 13.G.230.237; 13.G.230.238; 13.G.230.239; 13.G.230.154; 13.G.230.157; 13.G.230.166; 13.G.230.169; 13.G.230.172; 13.G.230.175; 13.G.230.240; 13.G.230.244; 13.G.231.228; 13.G.231.229; 13.G.231.230; 13.G.231.231; 13.G.231.236; 13.G.231.237; 13.G.231.238; 13.G.231.239; 13.G.231.154; 13.G.231.157; 13.G.231.166; 13.G.231.169; 13.G.231.172; 13.G.231.175; 13.G.231.240; 13.G.231.244; 13.G.236.228; 13.G.236.229; 13.G.236.230; 13.G.236.231; 13.G.236.236; 13.G.236.237; 13.G.236.238; 13.G.236.239; 13.G.236.154; 13.G.236.157; 13.G.236.166; 13.G.236.169; 13.G.236.172; 13.G.236.175; 13.G.236.240; 13.G.236.244; 13.G.237.228; 13.G.237.229; 13.G.237.230; 13.G.237.231; 13.G.237.236; 13.G.237.237; 13.G.237.238; 13.G.237.239; 13.G.237.154; 13.G.237.157; 13.G.237.166; 13.G.237.169; 13.G.237.172; 13.G.237.175; 13.G.237.240; 13.G.237.244; 13.G.238.228; 13.G.238.229; 13.G.238.230; 13.G.238.231; 13.G.238.236; 13.G.238.237; 13.G.238.238; 13.G.238.239; 13.G.238.154; 13.G.238.157; 13.G.238.166; 13.G.238.169; 13.G.238.172; 13.G.238.175; 13.G.238.240; 13.G.238.244; 13.G.239.228; 13.G.239.229; 13.G.239.230; 13.G.239.231; 13.G.239.236; 13.G.239.237; 13.G.239.238; 13.G.239.239; 13.G.239.154; 13.G.239.157; 13.G.239.166; 13.G.239.169; 13.G.239.172; 13.G.239.175; 13.G.239.240; 13.G.239.244; 13.G.154.228; 13.G.154.229; 13.G.154.230; 13.G.154.231; 13.G.154.236; 13.G.154.237; 13.G.154.238; 13.G.154.239; 13.G.154.154; 13.G.154.157; 13.G.154.166; 13.G.154.169; 13.G.154.172; 13.G.154.175; 13.G.154.240; 13.G.154.244; 13.G.157.228; 13.G.157.229; 13.G.157.230; 13.G.157.231; 13.G.157.236; 13.G.157.237; 13.G.157.238; 13.G.157.239; 13.G.157.154; 13.G.157.157; 13.G.157.166; 13.G.157.169; 13.G.157.172; 13.G.157.175; 13.G.157.240; 13.G.157.244; 13.G.166.228; 13.G.166.229; 13.G.166.230; 13.G.166.231; 13.G.166.236; 13.G.166.237; 13.G.166.238; 13.G.166.239; 13.G.166.154; 13.G.166.157; 13.G.166.166; 13.G.166.169; 13.G.166.172; 13.G.166.175; 13.G.166.240; 13.G.166.244; 13.G.169.228; 13.G.169.229; 13.G.169.230; 13.G.169.231; 13.G.169.236; 13.G.169.237; 13.G.169.238; 13.G.169.239; 13.G.169.154; 13.G.169.157; 13.G.169.166; 13.G.169.169; 13.G.169.172; 13.G.169.175; 13.G.169.240; 13.G.169.244; 13.G.172.228; 13.G.172.229; 13.G.172.230; 13.G.172.231; 13.G.172.236; 13.G.172.237; 13.G.172.238; 13.G.172.239; 13.G.172.154; 13.G.172.157; 13.G.172.166; 13.G.172.169; 13.G.172.172; 13.G.172.175; 13.G.172.240; 13.G.172.244; 13.G.175.228; 13.G.175.229; 13.G.175.230; 13.G.175.231; 13.G.175.236; 13.G.175.237; 13.G.175.238; 13.G.175.239; 13.G.175.154; 13.G.175.157; 13.G.175.166; 13.G.175.169; 13.G.175.172; 13.G.175.175; 13.G.175.240; 13.G.175.244; 13.G.240.228; 13.G.240.229; 13.G.240.230; 13.G.240.231; 13.G.240.236; 13.G.240.237; 13.G.240.238; 13.G.240.239; 13.G.240.154; 13.G.240.157; 13.G.240.166; 13.G.240.169; 13.G.240.172; 13.G.240.175; 13.G.240.240; 13.G.240.244; 13.G.244.228; 13.G.244.229; 13.G.244.230; 13.G.244.231; 13.G.244.236; 13.G.244.237; 13.G.244.238; 13.G.244.239; 13.G.244.154; 13.G.244.157; 13.G.244.166; 13.G.244.169; 13.G.244.172; 13.G.244.175; 13.G.244.240; 13.G.244.244;

<u>Prodrugs of 13.I</u>

13.I.228.228; 13.I.228.229; 13.I.228.230; 13.I.228.231; 13.I.228.236; 13.I.228.237; 13.I.228.238; 13.I.228.239; 13.I.228.154; 13.I.228.157; 13.I.228.166; 13.I.228.169; 13.I.228.172; 13.I.228.175; 13.I.228.240; 13.I.228.244; 13.I.229.228; 13.I.229.229; 13.I.229.230; 13.I.229.231; 13.I.229.236; 13.I.229.237; 13.I.229.238; 13.I.229.239; 13.I.229.154; 13.I.229.157; 13.I.229.166; 13.I.229.169; 13.I.229.172; 13.I.229.175; 13.I.229.240; 13.I.229.244; 13.I.230.228; 13.I.230.229; 13.I.230.230; 13.I.230.231; 13.I.230.236; 13.I.230.237; 13.I.230.238; 13.I.230.239; 13.I.230.154; 13.I.230.157; 13.I.230.166; 13.I.230.169; 13.I.230.172; 13.I.230.175; 13.I.230.240; 13.I.230.244; 13.I.231.228; 13.I.231.229; 13.I.231.230; 13.I.231.231; 13.I.231.236; 13.I.231.237; 13.I.231.238; 13.I.231.239; 13.I.231.154; 13.I.231.157; 13.I.231.166; 13.I.231.169; 13.I.231.172; 13.I.231.175; 13.I.231.240; 13.I.231.244; 13.I.236.228; 13.I.236.229; 13.I.236.230; 13.I.236.231; 13.I.236.236; 13.I.236.237; 13.I.236.238; 13.I.236.239; 13.I.236.154; 13.I.236.157; 13.I.236.166; 13.I.236.169; 13.I.236.172; 13.I.236.175; 13.I.236.240; 13.I.236.244; 13.I.237.228; 13.I.237.229; 13.I.237.230; 13.I.237.231; 13.I.237.236; 13.I.237.237; 13.I.237.238; 13.I.237.239; 13.I.237.154; 13.I.237.157; 13.I.237.166; 13.I.237.169; 13.I.237.172; 13.I.237.175; 13.I.237.240; 13.I.237.244; 13.I.238.228; 13.I.238.229; 13.I.238.230; 13.I.238.231; 13.I.238.236; 13.I.238.237; 13.I.238.238; 13.I.238.239; 13.I.238.154; 13.I.238.157; 13.I.238.166; 13.I.238.169; 13.I.238.172; 13.I.238.175; 13.I.238.240; 13.I.238.244; 13.I.239.228; 13.I.239.229; 13.I.239.230; 13.I.239.231; 13.I.239.236; 13.I.239.237; 13.I.239.238; 13.I.239.239; 13.I.239.154; 13.I.239.157; 13.I.239.166; 13.I.239.169; 13.I.239.172; 13.I.239.175; 13.I.239.240; 13.I.239.244; 13.I.154.228; 13.I.154.229; 13.I.154.230; 13.I.154.231; 13.I.154.236; 13.I.154.237; 13.I.154.238; 13.I.154.239; 13.I.154.154; 13.I.154.157; 13.I.154.166; 13.I.154.169; 13.I.154.172; 13.I.154.175; 13.I.154.240; 13.I.154.244; 13.I.157.228; 13.I.157.229; 13.I.157.230; 13.I.157.231; 13.I.157.236; 13.I.157.237; 13.I.157.238; 13.I.157.239; 13.I.157.154; 13.I.157.157; 13.I.157.166; 13.I.157.169; 13.I.157.172; 13.I.157.175; 13.I.157.240; 13.I.157.244; 13.I.166.228; 13.I.166.229; 13.I.166.230; 13.I.166.231; 13.I.166.236; 13.I.166.237; 13.I.166.238; 13.I.166.239; 13.I.166.154; 13.I.166.157; 13.I.166.166; 13.I.166.169; 13.I.166.172; 13.I.166.175; 13.I.166.240; 13.I.166.244; 13.I.169.228; 13.I.169.229; 13.I.169.230; 13.I.169.231; 13.I.169.236; 13.I.169.237; 13.I.169.238; 13.I.169.239; 13.I.169.154; 13.I.169.157; 13.I.169.166; 13.I.169.169; 13.I.169.172; 13.I.169.175; 13.I.169.240; 13.I.169.244; 13.I.172.228; 13.I.172.229; 13.I.172.230; 13.I.172.231; 13.I.172.236; 13.I.172.237; 13.I.172.238; 13.I.172.239; 13.I.172.154; 13.I.172.157; 13.I.172.166; 13.I.172.169; 13.I.172.172; 13.I.172.175; 13.I.172.240; 13.I.172.244; 13.I.175.228; 13.I.175.229; 13.I.175.230; 13.I.175.231; 13.I.175.236; 13.I.175.237; 13.I.175.238; 13.I.175.239; 13.I.175.154; 13.I.175.157; 13.I.175.166; 13.I.175.169; 13.I.175.172; 13.I.175.175; 13.I.175.240; 13.I.175.244; 13.I.240.228; 13.I.240.229; 13.I.240.230; 13.I.240.231; 13.I.240.236; 13.I.240.237; 13.I.240.238; 13.I.240.239; 13.I.240.154; 13.I.240.157; 13.I.240.166; 13.I.240.169; 13.I.240.172; 13.I.240.175; 13.I.240.240; 13.I.240.244; 13.I.244.228; 13.I.244.229; 13.I.244.230; 13.I.244.231; 13.I.244.236; 13.I.244.237; 13.I.244.238; 13.I.244.239; 13.I.244.154; 13.I.244.157; 13.I.244.166; 13.I.244.169; 13.I.244.172; 13.I.244.175; 13.I.244.240; 13.I.244.244;

<u>Prodrugs of 13.I</u>

13.J.228.228; 13.J.228.229; 13.J.228.230; 13.J.228.231; 13.J.228.236; 13.J.228.237; 13.J.228.238; 13.J.228.239; 13.J.228.154; 13.J.228.157; 13.J.228.166; 13.J.228.169; 13.J.228.172; 13.J.228.175; 13.J.228.240; 13.J.228.244; 13.J.229.228; 13.J.229.229; 13.J.229.230; 13.J.229.231; 13.J.229.236; 13.J.229.237; 13.J.229.238; 13.J.229.239; 13.J.229.154; 13.J.229.157; 13.J.229.166; 13.J.229.169; 13.J.229.172; 13.J.229.175; 13.J.229.240; 13.J.229.244; 13.J.230.228; 13.J.230.229; 13.J.230.230; 13.J.230.231; 13.J.230.236; 13.J.230.237; 13.J.230.238; 13.J.230.239; 13.J.230.154; 13.J.230.157; 13.J.230.166; 13.J.230.169; 13.J.230.172; 13.J.230.175; 13.J.230.240; 13.J.230.244; 13.J.231.228; 13.J.231.229; 13.J.231.230; 13.J.231.231; 13.J.231.236; 13.J.231.237; 13.J.231.238; 13.J.231.239; 13.J.231.154; 13.J.231.157; 13.J.231.166; 13.J.231.169; 13.J.231.172; 13.J.231.175; 13.J.231.240; 13.J.231.244; 13.J.236.228; 13.J.236.229; 13.J.236.230; 13.J.236.231; 13.J.236.236; 13.J.236.237; 13.J.236.238; 13.J.236.239; 13.J.236.154; 13.J.236.157; 13.J.236.166; 13.J.236.169; 13.J.236.172; 13.J.236.175; 13.J.236.240; 13.J.236.244; 13.J.237.228; 13.J.237.229; 13.J.237.230; 13.J.237.231; 13.J.237.236; 13.J.237.237; 13.J.237.238; 13.J.237.239; 13.J.237.154; 13.J.237.157; 13.J.237.166; 13.J.237.169; 13.J.237.172; 13.J.237.175; 13.J.237.240; 13.J.237.244; 13.J.238.228; 13.J.238.229; 13.J.238.230; 13.J.238.231; 13.J.238.236; 13.J.238.237; 13.J.238.238; 13.J.238.239; 13.J.238.154; 13.J.238.157; 13.J.238.166; 13.J.238.169; 13.J.238.172; 13.J.238.175; 13.J.238.240; 13.J.238.244; 13.J.239.228; 13.J.239.229; 13.J.239.230; 13.J.239.231; 13.J.239.236; 13.J.239.237; 13.J.239.238; 13.J.239.239; 13.J.239.154; 13.J.239.157; 13.J.239.166; 13.J.239.169; 13.J.239.172; 13.J.239.175; 13.J.239.240; 13.J.239.244; 13.J.154.228; 13.J.154.229; 13.J.154.230; 13.J.154.231; 13.J.154.236; 13.J.154.237; 13.J.154.238; 13.J.154.239; 13.J.154.154; 13.J.154.157; 13.J.154.166; 13.J.154.169; 13.J.154.172; 13.J.154.175; 13.J.154.240; 13.J.154.244; 13.J.157.228; 13.J.157.229; 13.J.157.230; 13.J.157.231; 13.J.157.236; 13.J.157.237; 13.J.157.238; 13.J.157.239; 13.J.157.154; 13.J.157.157; 13.J.157.166; 13.J.157.169; 13.J.157.172; 13.J.157.175; 13.J.157.240; 13.J.157.244; 13.J.166.228; 13.J.166.229; 13.J.166.230; 13.J.166.231; 13.J.166.236; 13.J.166.237; 13.J.166.238; 13.J.166.239; 13.J.166.154; 13.J.166.157; 13.J.166.166; 13.J.166.169; 13.J.166.172; 13.J.166.175; 13.J.166.240; 13.J.166.244; 13.J.169.228; 13.J.169.229; 13.J.169.230; 13.J.169.231; 13.J.169.236; 13.J.169.237; 13.J.169.238; 13.J.169.239; 13.J.169.154; 13.J.169.157; 13.J.169.166; 13.J.169.169; 13.J.169.172; 13.J.169.175; 13.J.169.240; 13.J.169.244; 13.J.172.228; 13.J.172.229; 13.J.172.230; 13.J.172.231; 13.J.172.236; 13.J.172.237; 13.J.172.238; 13.J.172.239; 13.J.172.154; 13.J.172.157; 13.J.172.166; 13.J.172.169; 13.J.172.172; 13.J.172.175; 13.J.172.240; 13.J.172.244; 13.J.175.228; 13.J.175.229; 13.J.175.230; 13.J.175.231; 13.J.175.236; 13.J.175.237; 13.J.175.238; 13.J.175.239; 13.J.175.154; 13.J.175.157; 13.J.175.166; 13.J.175.169; 13.J.175.172; 13.J.175.175; 13.J.175.240; 13.J.175.244; 13.J.240.228; 13.J.240.229; 13.J.240.230; 13.J.240.231; 13.J.240.236; 13.J.240.237; 13.J.240.238; 13.J.240.239; 13.J.240.154; 13.J.240.157; 13.J.240.166; 13.J.240.169; 13.J.240.172; 13.J.240.175; 13.J.240.240; 13.J.240.244; 13.J.244.228; 13.J.244.229; 13.J.244.230; 13.J.244.231; 13.J.244.236; 13.J.244.237; 13.J.244.238; 13.J.244.239; 13.J.244.154; 13.J.244.157; 13.J.244.166; 13.J.244.169; 13.J.244.172; 13.J.244.175; 13.J.244.240; 13.J.244.244;

Prodrugs of 13.L

13.L.228.228; 13.L.228.229; 13.L.228.230; 13.L.228.231; 13.L.228.236; 13.L.228.237; 13.L.228.238; 13.L.228.239; 13.L.228.154; 13.L.228.157; 13.L.228.166; 13.L.228.169; 13.L.228.172; 13.L.228.175; 13.L.228.240; 13.L.228.244; 13.L.229.228; 13.L.229.229; 13.L.229.230; 13.L.229.231; 13.L.229.236; 13.L.229.237; 13.L.229.238; 13.L.229.239; 13.L.229.154; 13.L.229.157; 13.L.229.166; 13.L.229.169; 13.L.229.172; 13.L.229.175; 13.L.229.240; 13.L.229.244; 13.L.230.228; 13.L.230.229; 13.L.230.230; 13.L.230.231; 13.L.230.236; 13.L.230.237; 13.L.230.238; 13.L.230.239; 13.L.230.154; 13.L.230.157; 13.L.230.166; 13.L.230.169; 13.L.230.172; 13.L.230.175; 13.L.230.240; 13.L.230.244; 13.L.231.228; 13.L.231.229; 13.L.231.230; 13.L.231.231; 13.L.231.236; 13.L.231.237; 13.L.231.238; 13.L.231.239; 13.L.231.154; 13.L.231.157; 13.L.231.166; 13.L.231.169; 13.L.231.172; 13.L.231.175; 13.L.231.240; 13.L.231.244; 13.L.236.228; 13.L.236.229; 13.L.236.230; 13.L.236.231; 13.L.236.236; 13.L.236.237; 13.L.236.238; 13.L.236.239; 13.L.236.154; 13.L.236.157; 13.L.236.166; 13.L.236.169; 13.L.236.172; 13.L.236.175; 13.L.236.240; 13.L.236.244; 13.L.237.228; 13.L.237.229; 13.L.237.230; 13.L.237.231; 13.L.237.236; 13.L.237.237; 13.L.237.238; 13.L.237.239; 13.L.237.154; 13.L.237.157; 13.L.237.166; 13.L.237.169; 13.L.237.172; 13.L.237.175; 13.L.237.240; 13.L.237.244; 13.L.238.228; 13.L.238.229; 13.L.238.230; 13.L.238.231; 13.L.238.236; 13.L.238.237; 13.L.238.238; 13.L.238.239; 13.L.238.154; 13.L.238.157; 13.L.238.166; 13.L.238.169; 13.L.238.172; 13.L.238.175; 13.L.238.240; 13.L.238.244; 13.L.239.228; 13.L.239.229; 13.L.239.230; 13.L.239.231; 13.L.239.236; 13.L.239.237; 13.L.239.238; 13.L.239.239; 13.L.239.154; 13.L.239.157; 13.L.239.166; 13.L.239.169; 13.L.239.172; 13.L.239.175; 13.L.239.240; 13.L.239.244; 13.L.154.228; 13.L.154.229; 13.L.154.230; 13.L.154.231; 13.L.154.236; 13.L.154.237; 13.L.154.238; 13.L.154.239; 13.L.154.154; 13.L.154.157; 13.L.154.166; 13.L.154.169; 13.L.154.172; 13.L.154.175; 13.L.154.240; 13.L.154.244; 13.L.157.228; 13.L.157.229; 13.L.157.230; 13.L.157.231; 13.L.157.236; 13.L.157.237; 13.L.157.238; 13.L.157.239; 13.L.157.154; 13.L.157.157; 13.L.157.166; 13.L.157.169; 13.L.157.172; 13.L.157.175; 13.L.157.240; 13.L.157.244; 13.L.166.228; 13.L.166.229; 13.L.166.230; 13.L.166.231; 13.L.166.236; 13.L.166.237; 13.L.166.238; 13.L.166.239; 13.L.166.154; 13.L.166.157; 13.L.166.166; 13.L.166.169; 13.L.166.172; 13.L.166.175; 13.L.166.240; 13.L.166.244; 13.L.169.228; 13.L.169.229; 13.L.169.230; 13.L.169.231; 13.L.169.236; 13.L.169.237; 13.L.169.238; 13.L.169.239; 13.L.169.154; 13.L.169.157; 13.L.169.166; 13.L.169.169; 13.L.169.172; 13.L.169.175; 13.L.169.240; 13.L.169.244; 13.L.172.228; 13.L.172.229; 13.L.172.230; 13.L.172.231; 13.L.172.236; 13.L.172.237; 13.L.172.238; 13.L.172.239; 13.L.172.154; 13.L.172.157; 13.L.172.166; 13.L.172.169; 13.L.172.172; 13.L.172.175; 13.L.172.240; 13.L.172.244; 13.L.175.228; 13.L.175.229; 13.L.175.230; 13.L.175.231; 13.L.175.236; 13.L.175.237; 13.L.175.238; 13.L.175.239; 13.L.175.154; 13.L.175.157; 13.L.175.166; 13.L.175.169; 13.L.175.172; 13.L.175.175; 13.L.175.240; 13.L.175.244; 13.L.240.228; 13.L.240.229; 13.L.240.230; 13.L.240.231; 13.L.240.236; 13.L.240.237; 13.L.240.238; 13.L.240.239; 13.L.240.154; 13.L.240.157; 13.L.240.166; 13.L.240.169; 13.L.240.172; 13.L.240.175; 13.L.240.240; 13.L.240.244; 13.L.244.228; 13.L.244.229; 13.L.244.230; 13.L.244.231; 13.L.244.236; 13.L.244.237; 13.L.244.238; 13.L.244.239; 13.L.244.154; 13.L.244.157; 13.L.244.166; 13.L.244.169; 13.L.244.172; 13.L.244.175; 13.L.244.240; 13.L.244.244;

Prodrugs of 13.O

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13.U.228.228; 13.U.228.229; 13.U.228.230; 13.U.228.231; 13.U.228.236; 13.U.228.237; 13.U.228.238; 13.U.228.239; 13.U.228.154; 13.U.228.157; 13.U.228.166; 13.U.228.169; 13.U.228.172; 13.U.228.175; 13.U.228.240; 13.U.228.244; 13.U.229.228; 13.U.229.229; 13.U.229.230; 13.U.229.231; 13.U.229.236; 13.U.229.237; 13.U.229.238; 13.U.229.239; 13.U.229.154; 13.U.229.157; 13.U.229.166; 13.U.229.169; 13.U.229.172; 13.U.229.175; 13.U.229.240; 13.U.229.244; 13.U.230.228; 13.U.230.229; 13.U.230.230; 13.U.230.231; 13.U.230.236; 13.U.230.237; 13.U.230.238; 13.U.230.239; 13.U.230.154; 13.U.230.157; 13.U.230.166; 13.U.230.169; 13.U.230.172; 13.U.230.175; 13.U.230.240; 13.U.230.244; 13.U.231.228; 13.U.231.229; 13.U.231.230; 13.U.231.231; 13.U.231.236; 13.U.231.237; 13.U.231.238; 13.U.231.239; 13.U.231.154; 13.U.231.157; 13.U.231.166; 13.U.231.169; 13.U.231.172; 13.U.231.175; 13.U.231.240; 13.U.231.244; 13.U.236.228; 13.U.236.229; 13.U.236.230; 13.U.236.231; 13.U.236.236; 13.U.236.237; 13.U.236.238; 13.U.236.239; 13.U.236.154; 13.U.236.157; 13.U.236.166; 13.U.236.169; 13.U.236.172; 13.U.236.175; 13.U.236.240; 13.U.236.244; 13.U.237.228; 13.U.237.229; 13.U.237.230; 13.U.237.231; 13.U.237.236; 13.U.237.237; 13.U.237.238; 13.U.237.239; 13.U.237.154; 13.U.237.157; 13.U.237.166; 13.U.237.169; 13.U.237.172; 13.U.237.175; 13.U.237.240; 13.U.237.244; 13.U.238.228; 13.U.238.229; 13.U.238.230; 13.U.238.231; 13.U.238.236; 13.U.238.237; 13.U.238.238; 13.U.238.239; 13.U.238.154; 13.U.238.157; 13.U.238.166; 13.U.238.169; 13.U.238.172; 13.U.238.175; 13.U.238.240; 13.U.238.244; 13.U.239.228; 13.U.239.229; 13.U.239.230; 13.U.239.231; 13.U.239.236; 13.U.239.237; 13.U.239.238; 13.U.239.239; 13.U.239.154; 13.U.239.157; 13.U.239.166; 13.U.239.169; 13.U.239.172; 13.U.239.175; 13.U.239.240; 13.U.239.244; 13.U.154.228; 13.U.154.229; 13.U.154.230; 13.U.154.231; 13.U.154.236; 13.U.154.237; 13.U.154.238; 13.U.154.239; 13.U.154.154; 13.U.154.157; 13.U.154.166; 13.U.154.169; 13.U.154.172; 13.U.154.175; 13.U.154.240; 13.U.154.244; 13.U.157.228; 13.U.157.229; 13.U.157.230; 13.U.157.231; 13.U.157.236; 13.U.157.237; 13.U.157.238; 13.U.157.239; 13.U.157.154; 13.U.157.157; 13.U.157.166; 13.U.157.169; 13.U.157.172; 13.U.157.175; 13.U.157.240; 13.U.157.244; 13.U.166.228; 13.U.166.229; 13.U.166.230; 13.U.166.231; 13.U.166.236; 13.U.166.237; 13.U.166.238; 13.U.166.239; 13.U.166.154; 13.U.166.157; 13.U.166.166; 13.U.166.169; 13.U.166.172; 13.U.166.175; 13.U.166.240; 13.U.166.244; 13.U.169.228; 13.U.169.229; 13.U.169.230; 13.U.169.231; 13.U.169.236; 13.U.169.237; 13.U.169.238; 13.U.169.239; 13.U.169.154; 13.U.169.157; 13.U.169.166; 13.U.169.169; 13.U.169.172; 13.U.169.175; 13.U.169.240; 13.U.169.244; 13.U.172.228; 13.U.172.229; 13.U.172.230; 13.U.172.231; 13.U.172.236; 13.U.172.237; 13.U.172.238; 13.U.172.239; 13.U.172.154; 13.U.172.157; 13.U.172.166; 13.U.172.169; 13.U.172.172; 13.U.172.175; 13.U.172.240; 13.U.172.244; 13.U.175.228; 13.U.175.229; 13.U.175.230; 13.U.175.231; 13.U.175.236; 13.U.175.237; 13.U.175.238; 13.U.175.239; 13.U.175.154; 13.U.175.157; 13.U.175.166; 13.U.175.169; 13.U.175.172; 13.U.175.175; 13.U.175.240; 13.U.175.244; 13.U.240.228; 13.U.240.229; 13.U.240.230; 13.U.240.231; 13.U.240.236; 13.U.240.237; 13.U.240.238; 13.U.240.239; 13.U.240.154; 13.U.240.157; 13.U.240.166; 13.U.240.169; 13.U.240.172; 13.U.240.175; 13.U.240.240; 13.U.240.244; 13.U.244.228; 13.U.244.229; 13.U.244.230; 13.U.244.231; 13.U.244.236; 13.U.244.237; 13.U.244.238; 13.U.244.239; 13.U.244.154; 13.U.244.157; 13.U.244.166; 13.U.244.169; 13.U.244.172; 13.U.244.175; 13.U.244.240; 13.U.244.244;

Prodrugs of 13.W

13.W.228.228; 13.W.228.229; 13.W.228.230; 13.W.228.231; 13.W.228.236; 13.W.228.237; 13.W.228.238; 13.W.228.239; 13.W.228.154; 13.W.228.157; 13.W.228.166; 13.W.228.169; 13.W.228.172; 13.W.228.175; 13.W.228.240; 13.W.228.244; 13.W.229.228; 13.W.229.229; 13.W.229.230; 13.W.229.231; 13.W.229.236; 13.W.229.237; 13.W.229.238; 13.W.229.239; 13.W.229.154; 13.W.229.157; 13.W.229.166; 13.W.229.169; 13.W.229.172; 13.W.229.175; 13.W.229.240; 13.W.229.244; 13.W.230.228; 13.W.230.229; 13.W.230.230; 13.W.230.231; 13.W.230.236; 13.W.230.237; 13.W.230.238; 13.W.230.239; 13.W.230.154; 13.W.230.157; 13.W.230.166; 13.W.230.169; 13.W.230.172; 13.W.230.175; 13.W.230.240; 13.W.230.244; 13.W.231.228; 13.W.231.229; 13.W.231.230; 13.W.231.231; 13.W.231.236; 13.W.231.237; 13.W.231.238; 13.W.231.239; 13.W.231.154; 13.W.231.157; 13.W.231.166; 13.W.231.169; 13.W.231.172; 13.W.231.175; 13.W.231.240; 13.W.231.244; 13.W.236.228; 13.W.236.229; 13.W.236.230; 13.W.236.231; 13.W.236.236; 13.W.236.237; 13.W.236.238; 13.W.236.239; 13.W.236.154; 13.W.236.157; 13.W.236.166; 13.W.236.169; 13.W.236.172; 13.W.236.175; 13.W.236.240; 13.W.236.244; 13.W.237.228; 13.W.237.229; 13.W.237.230; 13.W.237.231; 13.W.237.236; 13.W.237.237; 13.W.237.238; 13.W.237.239; 13.W.237.154; 13.W.237.157; 13.W.237.166; 13.W.237.169; 13.W.237.172; 13.W.237.175; 13.W.237.240; 13.W.237.244; 13.W.238.228; 13.W.238.229; 13.W.238.230; 13.W.238.231; 13.W.238.236; 13.W.238.237; 13.W.238.238; 13.W.238.239; 13.W.238.154; 13.W.238.157; 13.W.238.166; 13.W.238.169; 13.W.238.172; 13.W.238.175; 13.W.238.240; 13.W.238.244; 13.W.239.228; 13.W.239.229; 13.W.239.230; 13.W.239.231; 13.W.239.236; 13.W.239.237; 13.W.239.238; 13.W.239.239; 13.W.239.154; 13.W.239.157; 13.W.239.166; 13.W.239.169; 13.W.239.172; 13.W.239.175; 13.W.239.240; 13.W.239.244; 13.W.154.228; 13.W.154.229; 13.W.154.230; 13.W.154.231; 13.W.154.236; 13.W.154.237; 13.W.154.238; 13.W.154.239; 13.W.154.154; 13.W.154.157; 13.W.154.166; 13.W.154.169; 13.W.154.172; 13.W.154.175; 13.W.154.240; 13.W.154.244; 13.W.157.228; 13.W.157.229; 13.W.157.230; 13.W.157.231; 13.W.157.236; 13.W.157.237; 13.W.157.238; 13.W.157.239; 13.W.157.154; 13.W.157.157; 13.W.157.166; 13.W.157.169; 13.W.157.172; 13.W.157.175; 13.W.157.240; 13.W.157.244; 13.W.166.228; 13.W.166.229; 13.W.166.230; 13.W.166.231; 13.W.166.236; 13.W.166.237; 13.W.166.238; 13.W.166.239; 13.W.166.154; 13.W.166.157; 13.W.166.166; 13.W.166.169; 13.W.166.172; 13.W.166.175; 13.W.166.240; 13.W.166.244; 13.W.169.228; 13.W.169.229; 13.W.169.230; 13.W.169.231; 13.W.169.236; 13.W.169.237; 13.W.169.238; 13.W.169.239; 13.W.169.154; 13.W.169.157; 13.W.169.166; 13.W.169.169; 13.W.169.172; 13.W.169.175; 13.W.169.240; 13.W.169.244; 13.W.172.228; 13.W.172.229; 13.W.172.230; 13.W.172.231; 13.W.172.236; 13.W.172.237; 13.W.172.238; 13.W.172.239; 13.W.172.154; 13.W.172.157; 13.W.172.166; 13.W.172.169; 13.W.172.172; 13.W.172.175; 13.W.172.240; 13.W.172.244; 13.W.175.228; 13.W.175.229; 13.W.175.230; 13.W.175.231; 13.W.175.236; 13.W.175.237; 13.W.175.238; 13.W.175.239; 13.W.175.154; 13.W.175.157; 13.W.175.166; 13.W.175.169; 13.W.175.172; 13.W.175.175; 13.W.175.240; 13.W.175.244; 13.W.240.228; 13.W.240.229; 13.W.240.230; 13.W.240.231; 13.W.240.236; 13.W.240.237; 13.W.240.238; 13.W.240.239; 13.W.240.154; 13.W.240.157; 13.W.240.166; 13.W.240.169; 13.W.240.172; 13.W.240.175; 13.W.240.240; 13.W.240.244; 13.W.244.228; 13.W.244.229; 13.W.244.230; 13.W.244.231; 13.W.244.236; 13.W.244.237; 13.W.244.238; 13.W.244.239; 13.W.244.154; 13.W.244.157; 13.W.244.166; 13.W.244.169; 13.W.244.172; 13.W.244.175; 13.W.244.240; 13.W.244.244;

Prodrugs of 13.Y

13.Y.228.228; 13.Y.228.229; 13.Y.228.230; 13.Y.228.231; 13.Y.228.236; 13.Y.228.237; 13.Y.228.238; 13.Y.228.239; 13.Y.228.154; 13.Y.228.157; 13.Y.228.166; 13.Y.228.169; 13.Y.228.172; 13.Y.228.175; 13.Y.228.240; 13.Y.228.244; 13.Y.229.228; 13.Y.229.229; 13.Y.229.230; 13.Y.229.231; 13.Y.229.236; 13.Y.229.237; 13.Y.229.238; 13.Y.229.239; 13.Y.229.154; 13.Y.229.157; 13.Y.229.166; 13.Y.229.169; 13.Y.229.172; 13.Y.229.175; 13.Y.229.240; 13.Y.229.244; 13.Y.230.228; 13.Y.230.229; 13.Y.230.230; 13.Y.230.231; 13.Y.230.236; 13.Y.230.237; 13.Y.230.238; 13.Y.230.239; 13.Y.230.154; 13.Y.230.157; 13.Y.230.166; 13.Y.230.169; 13.Y.230.172; 13.Y.230.175; 13.Y.230.240; 13.Y.230.244; 13.Y.231.228; 13.Y.231.229; 13.Y.231.230; 13.Y.231.231; 13.Y.231.236; 13.Y.231.237; 13.Y.231.238; 13.Y.231.239; 13.Y.231.154; 13.Y.231.157; 13.Y.231.166; 13.Y.231.169; 13.Y.231.172; 13.Y.231.175; 13.Y.231.240; 13.Y.231.244; 13.Y.236.228; 13.Y.236.229; 13.Y.236.230; 13.Y.236.231; 13.Y.236.236; 13.Y.236.237; 13.Y.236.238; 13.Y.236.239; 13.Y.236.154; 13.Y.236.157; 13.Y.236.166; 13.Y.236.169; 13.Y.236.172; 13.Y.236.175; 13.Y.236.240; 13.Y.236.244; 13.Y.237.228; 13.Y.237.229; 13.Y.237.230; 13.Y.237.231; 13.Y.237.236; 13.Y.237.237; 13.Y.237.238; 13.Y.237.239; 13.Y.237.154; 13.Y.237.157; 13.Y.237.166; 13.Y.237.169; 13.Y.237.172; 13.Y.237.175; 13.Y.237.240; 13.Y.237.244; 13.Y.238.228; 13.Y.238.229; 13.Y.238.230; 13.Y.238.231; 13.Y.238.236; 13.Y.238.237; 13.Y.238.238; 13.Y.238.239; 13.Y.238.154; 13.Y.238.157; 13.Y.238.166; 13.Y.238.169; 13.Y.238.172; 13.Y.238.175; 13.Y.238.240; 13.Y.238.244; 13.Y.239.228; 13.Y.239.229; 13.Y.239.230; 13.Y.239.231; 13.Y.239.236; 13.Y.239.237; 13.Y.239.238; 13.Y.239.239; 13.Y.239.154; 13.Y.239.157; 13.Y.239.166; 13.Y.239.169; 13.Y.239.172; 13.Y.239.175; 13.Y.239.240; 13.Y.239.244; 13.Y.154.228; 13.Y.154.229; 13.Y.154.230; 13.Y.154.231; 13.Y.154.236; 13.Y.154.237; 13.Y.154.238; 13.Y.154.239; 13.Y.154.154; 13.Y.154.157; 13.Y.154.166; 13.Y.154.169; 13.Y.154.172; 13.Y.154.175; 13.Y.154.240; 13.Y.154.244; 13.Y.157.228; 13.Y.157.229; 13.Y.157.230; 13.Y.157.231; 13.Y.157.236; 13.Y.157.237; 13.Y.157.238; 13.Y.157.239; 13.Y.157.154; 13.Y.157.157; 13.Y.157.166; 13.Y.157.169; 13.Y.157.172; 13.Y.157.175; 13.Y.157.240; 13.Y.157.244; 13.Y.166.228; 13.Y.166.229; 13.Y.166.230; 13.Y.166.231; 13.Y.166.236; 13.Y.166.237; 13.Y.166.238; 13.Y.166.239; 13.Y.166.154; 13.Y.166.157; 13.Y.166.166; 13.Y.166.169; 13.Y.166.172; 13.Y.166.175; 13.Y.166.240; 13.Y.166.244; 13.Y.169.228; 13.Y.169.229; 13.Y.169.230; 13.Y.169.231; 13.Y.169.236; 13.Y.169.237; 13.Y.169.238; 13.Y.169.239; 13.Y.169.154; 13.Y.169.157; 13.Y.169.166; 13.Y.169.169; 13.Y.169.172; 13.Y.169.175; 13.Y.169.240; 13.Y.169.244; 13.Y.172.228; 13.Y.172.229; 13.Y.172.230; 13.Y.172.231; 13.Y.172.236; 13.Y.172.237; 13.Y.172.238; 13.Y.172.239; 13.Y.172.154; 13.Y.172.157; 13.Y.172.166; 13.Y.172.169; 13.Y.172.172; 13.Y.172.175; 13.Y.172.240; 13.Y.172.244; 13.Y.175.228; 13.Y.175.229; 13.Y.175.230; 13.Y.175.231; 13.Y.175.236; 13.Y.175.237; 13.Y.175.238; 13.Y.175.239; 13.Y.175.154; 13.Y.175.157; 13.Y.175.166; 13.Y.175.169; 13.Y.175.172; 13.Y.175.175; 13.Y.175.240; 13.Y.175.244; 13.Y.240.228; 13.Y.240.229; 13.Y.240.230; 13.Y.240.231; 13.Y.240.236; 13.Y.240.237; 13.Y.240.238; 13.Y.240.239; 13.Y.240.154; 13.Y.240.157; 13.Y.240.166; 13.Y.240.169; 13.Y.240.172; 13.Y.240.175; 13.Y.240.240; 13.Y.240.244; 13.Y.244.228; 13.Y.244.229; 13.Y.244.230; 13.Y.244.231; 13.Y.244.236; 13.Y.244.237; 13.Y.244.238; 13.Y.244.239; 13.Y.244.154; 13.Y.244.157; 13.Y.244.166; 13.Y.244.169; 13.Y.244.172; 13.Y.244.175; 13.Y.244.240; 13.Y.244.244;

Prodrugs of 14.AH

14.AH.4.157; 14.AH.4.158; 14.AH.4.196; 14.AH.4.223; 14.AH.4.240; 14.AH.4.244; 14.AH.4.243; 14.AH.4.247; 14.AH.5.157; 14.AH.5.158; 14.AH.5.196; 14.AH.5.223; 14.AH.5.240; 14.AH.5.244; 14.AH.5.243; 14.AH.5.247; 14.AH.7.157; 14.AH.7.158; 14.AH.7.196; 14.AH.7.223; 14.AH.7.240; 14.AH.7.244; 14.AH.7.243; 14.AH.7.247; 14.AH.15.157; 14.AH.15.158; 14.AH.15.196; 14.AH.15.223; 14.AH.15.240; 14.AH.15.244; 14.AH.15.243; 14.AH.15.247; 14.AH.16.157; 14.AH.16.158; 14.AH.16.196; 14.AH.16.223; 14.AH.16.240; 14.AH.16.244; 14.AH.16.243; 14.AH.16.247; 14.AH.18.157; 14.AH.18.158; 14.AH.18.196; 14.AH.18.223; 14.AH.18.240; 14.AH.18.244; 14.AH.18.243; 14.AH.18.247; 14.AH.26.157; 14.AH.26.158; 14.AH.26.196; 14.AH.26.223; 14.AH.26.240; 14.AH.26.244; 14.AH.26.243; 14.AH.26.247; 14.AH.27.157; 14.AH.27.158; 14.AH.27.196; 14.AH.27.223; 14.AH.27.240; 14.AH.27.244; 14.AH.27.243; 14.AH.27.247; 14.AH.29.157; 14.AH.29.158; 14.AH.29.196; 14.AH.29.223; 14.AH.29.240; 14.AH.29.244; 14.AH.29.243; 14.AH.29.247; 14.AH.54.157; 14.AH.54.158; 14.AH.54.196; 14.AH.54.223; 14.AH.54.240; 14.AH.54.244; 14.AH.54.243; 14.AH.54.247; 14.AH.55.157; 14.AH.55.158; 14.AH.55.196; 14.AH.55.223; 14.AH.55.240; 14.AH.55.244; 14.AH.55.243; 14.AH.55.247; 14.AH.56.157; 14.AH.56.158; 14.AH.56.196; 14.AH.56.223; 14.AH.56.240; 14.AH.56.244; 14.AH.56.243; 14.AH.56.247; 14.AH.157.157; 14.AH.157.158; 14.AH.157.196; 14.AH.157.223; 14.AH.157.240; 14.AH.157.244; 14.AH.157.243; 14.AH.157.247; 14.AH.196.157; 14.AH.196.158; 14.AH.196.196; 14.AH.196.223; 14.AH.196.240; 14.AH.196.244; 14.AH.196.243; 14.AH.196.247; 14.AH.223.157; 14.AH.223.158; 14.AH.223.196; 14.AH.223.223; 14.AH.223.240; 14.AH.223.244; 14.AH.223.243; 14.AH.223.247; 14.AH.240.157; 14.AH.240.158; 14.AH.240.196; 14.AH.240.223; 14.AH.240.240; 14.AH.240.244; 14.AH.240.243; 14.AH.240.247; 14.AH.244.157; 14.AH.244.158; 14.AH.244.196; 14.AH.244.223; 14.AH.244.240; 14.AH.244.244; 14.AH.244.243; 14.AH.244.247; 14.AH.247.157; 14.AH.247.158; 14.AH.247.196; 14.AH.247.223; 14.AH.247.240; 14.AH.247.244; 14.AH.247.243; 14.AH.247.247;

Prodrugs of 14.AJ

14.AJ.4.157; 14.AJ.4.158; 14.AJ.4.196; 14.AJ.4.223; 14.AJ.4.240; 14.AJ.4.244; 14.AJ.4.243; 14.AJ.4.247; 14.AJ.5.157; 14.AJ.5.158; 14.AJ.5.196; 14.AJ.5.223; 14.AJ.5.240; 14.AJ.5.244; 14.AJ.5.243; 14.AJ.5.247; 14.AJ.7.157; 14.AJ.7.158; 14.AJ.7.196; 14.AJ.7.223; 14.AJ.7.240; 14.AJ.7.244; 14.AJ.7.243; 14.AJ.7.247; 14.AJ.15.157; 14.AJ.15.158; 14.AJ.15.196; 14.AJ.15.223; 14.AJ.15.240; 14.AJ.15.244; 14.AJ.15.243; 14.AJ.15.247; 14.AJ.16.157; 14.AJ.16.158; 14.AJ.16.196; 14.AJ.16.223; 14.AJ.16.240; 14.AJ.16.244; 14.AJ.16.243; 14.AJ.16.247; 14.AJ.18.157; 14.AJ.18.158; 14.AJ.18.196; 14.AJ.18.223; 14.AJ.18.240; 14.AJ.18.244; 14.AJ.18.243; 14.AJ.18.247; 14.AJ.26.157; 14.AJ.26.158; 14.AJ.26.196; 14.AJ.26.223; 14.AJ.26.240; 14.AJ.26.244; 14.AJ.26.243; 14.AJ.26.247; 14.AJ.27.157; 14.AJ.27.158; 14.AJ.27.196; 14.AJ.27.223; 14.AJ.27.240; 14.AJ.27.244; 14.AJ.27.243; 14.AJ.27.247; 14.AJ.29.157; 14.AJ.29.158; 14.AJ.29.196; 14.AJ.29.223; 14.AJ.29.240; 14.AJ.29.244; 14.AJ.29.243; 14.AJ.29.247; 14.AJ.54.157; 14.AJ.54.158; 14.AJ.54.196; 14.AJ.54.223; 14.AJ.54.240; 14.AJ.54.244; 14.AJ.54.243; 14.AJ.54.247; 14.AJ.55.157; 14.AJ.55.158; 14.AJ.55.196; 14.AJ.55.223; 14.AJ.55.240; 14.AJ.55.244; 14.AJ.55.243; 14.AJ.55.247; 14.AJ.56.157; 14.AJ.56.158; 14.AJ.56.196; 14.AJ.56.223; 14.AJ.56.240; 14.AJ.56.244; 14.AJ.56.243; 14.AJ.56.247; 14.AJ.157.157; 14.AJ.157.158; 14.AJ.157.196; 14.AJ.157.223; 14.AJ.157.240; 14.AJ.157.244; 14.AJ.157.243; 14.AJ.157.247; 14.AJ.196.157; 14.AJ.196.158; 14.AJ.196.196; 14.AJ.196.223;

14.AJ.196.240; 14.AJ.196.244; 14.AJ.196.243; 14.AJ.196.247; 14.AJ.223.157; 14.AJ.223.158; 14.AJ.223.196; 14.AJ.223.223; 14.AJ.223.240; 14.AJ.223.244; 14.AJ.223.243; 14.AJ.223.247; 14.AJ.240.157; 14.AJ.240.158; 14.AJ.240.196; 14.AJ.240.223; 14.AJ.240.240; 14.AJ.240.244; 14.AJ.240.243; 14.AJ.240.247; 14.AJ.244.157; 14.AJ.244.158; 14.AJ.244.196; 14.AJ.244.223; 14.AJ.244.240; 14.AJ.244.244; 14.AJ.244.243; 14.AJ.244.247; 14.AJ.247.157; 14.AJ.247.158; 14.AJ.247.196; 14.AJ.247.223; 14.AJ.247.240; 14.AJ.247.244; 14.AJ.247.243; 14.AJ.247.247;

Prodrugs of 14.AN

14.AN.4.157; 14.AN.4.158; 14.AN.4.196; 14.AN.4.223; 14.AN.4.240; 14.AN.4.244; 14.AN.4.243; 14.AN.4.247; 14.AN.5.157; 14.AN.5.158; 14.AN.5.196; 14.AN.5.223; 14.AN.5.240; 14.AN.5.244; 14.AN.5.243; 14.AN.5.247; 14.AN.7.157; 14.AN.7.158; 14.AN.7.196; 14.AN.7.223; 14.AN.7.240; 14.AN.7.244; 14.AN.7.243; 14.AN.7.247; 14.AN.15.157; 14.AN.15.158; 14.AN.15.196; 14.AN.15.223; 14.AN.15.240; 14.AN.15.244; 14.AN.15.243; 14.AN.15.247; 14.AN.16.157; 14.AN.16.158; 14.AN.16.196; 14.AN.16.223; 14.AN.16.240; 14.AN.16.244; 14.AN.16.243; 14.AN.16.247; 14.AN.18.157; 14.AN.18.158; 14.AN.18.196; 14.AN.18.223; 14.AN.18.240; 14.AN.18.244; 14.AN.18.243; 14.AN.18.247; 14.AN.26.157; 14.AN.26.158; 14.AN.26.196; 14.AN.26.223; 14.AN.26.240; 14.AN.26.244; 14.AN.26.243; 14.AN.26.247; 14.AN.27.157; 14.AN.27.158; 14.AN.27.196; 14.AN.27.223; 14.AN.27.240; 14.AN.27.244; 14.AN.27.243; 14.AN.27.247; 14.AN.29.157; 14.AN.29.158; 14.AN.29.196; 14.AN.29.223; 14.AN.29.240; 14.AN.29.244; 14.AN.29.243; 14.AN.29.247; 14.AN.54.157; 14.AN.54.158; 14.AN.54.196; 14.AN.54.223; 14.AN.54.240; 14.AN.54.244; 14.AN.54.243; 14.AN.54.247; 14.AN.55.157; 14.AN.55.158; 14.AN.55.196; 14.AN.55.223; 14.AN.55.240; 14.AN.55.244; 14.AN.55.243; 14.AN.55.247; 14.AN.56.157; 14.AN.56.158; 14.AN.56.196; 14.AN.56.223; 14.AN.56.240; 14.AN.56.244; 14.AN.56.243; 14.AN.56.247; 14.AN.157.157; 14.AN.157.158; 14.AN.157.196; 14.AN.157.223; 14.AN.157.240; 14.AN.157.244; 14.AN.157.243; 14.AN.157.247; 14.AN.196.157; 14.AN.196.158; 14.AN.196.196; 14.AN.196.223; 14.AN.196.240; 14.AN.196.244; 14.AN.196.243; 14.AN.196.247; 14.AN.223.157; 14.AN.223.158; 14.AN.223.196; 14.AN.223.223; 14.AN.223.240; 14.AN.223.244; 14.AN.223.243; 14.AN.223.247; 14.AN.240.157; 14.AN.240.158; 14.AN.240.196; 14.AN.240.223; 14.AN.240.240; 14.AN.240.244; 14.AN.240.243; 14.AN.240.247; 14.AN.244.157; 14.AN.244.158; 14.AN.244.196; 14.AN.244.223; 14.AN.244.240; 14.AN.244.244; 14.AN.244.243; 14.AN.244.247; 14.AN.247.157; 14.AN.247.158; 14.AN.247.196; 14.AN.247.223; 14.AN.247.240; 14.AN.247.244; 14.AN.247.243; 14.AN.247.247;

Prodrugs of 14.AP

14.AP.4.157; 14.AP.4.158; 14.AP.4.196; 14.AP.4.223; 14.AP.4.240; 14.AP.4.244; 14.AP.4.243; 14.AP.4.247; 14.AP.5.157; 14.AP.5.158; 14.AP.5.196; 14.AP.5.223; 14.AP.5.240; 14.AP.5.244; 14.AP.5.243; 14.AP.5.247; 14.AP.7.157; 14.AP.7.158; 14.AP.7.196; 14.AP.7.223; 14.AP.7.240; 14.AP.7.244; 14.AP.7.243; 14.AP.7.247; 14.AP.15.157; 14.AP.15.158; 14.AP.15.196; 14.AP.15.223; 14.AP.15.240; 14.AP.15.244; 14.AP.15.243; 14.AP.15.247; 14.AP.16.157; 14.AP.16.158; 14.AP.16.196; 14.AP.16.223; 14.AP.16.240; 14.AP.16.244; 14.AP.16.243; 14.AP.16.247; 14.AP.18.157; 14.AP.18.158; 14.AP.18.196; 14.AP.18.223; 14.AP.18.240; 14.AP.18.244; 14.AP.18.243; 14.AP.18.247; 14.AP.26.157; 14.AP.26.158; 14.AP.26.196; 14.AP.26.223; 14.AP.26.240; 14.AP.26.244; 14.AP.26.243; 14.AP.26.247; 14.AP.27.157; 14.AP.27.158; 14.AP.27.196; 14.AP.27.223;

14.AP.27.240; 14.AP.27.244; 14.AP.27.243; 14.AP.27.247; 14.AP.29.157; 14.AP.29.158; 14.AP.29.196; 14.AP.29.223; 14.AP.29.240; 14.AP.29.244; 14.AP.29.243; 14.AP.29.247; 14.AP.54.157; 14.AP.54.158; 14.AP.54.196; 14.AP.54.223; 14.AP.54.240; 14.AP.54.244; 14.AP.54.243; 14.AP.54.247; 14.AP.55.157; 14.AP.55.158; 14.AP.55.196; 14.AP.55.223; 14.AP.55.240; 14.AP.55.244; 14.AP.55.243; 14.AP.55.247; 14.AP.56.157; 14.AP.56.158; 14.AP.56.196; 14.AP.56.223; 14.AP.56.240; 14.AP.56.244; 14.AP.56.243; 14.AP.56.247; 14.AP.157.157; 14.AP.157.158; 14.AP.157.196; 14.AP.157.223; 14.AP.157.240; 14.AP.157.244; 14.AP.157.243; 14.AP.157.247; 14.AP.196.157; 14.AP.196.158; 14.AP.196.196; 14.AP.196.223; 14.AP.196.240; 14.AP.196.244; 14.AP.196.243; 14.AP.196.247; 14.AP.223.157; 14.AP.223.158; 14.AP.223.196; 14.AP.223.223; 14.AP.223.240; 14.AP.223.244; 14.AP.223.243; 14.AP.223.247; 14.AP.240.157; 14.AP.240.158; 14.AP.240.196; 14.AP.240.223; 14.AP.240.240; 14.AP.240.244; 14.AP.240.243; 14.AP.240.247; 14.AP.244.157; 14.AP.244.158; 14.AP.244.196; 14.AP.244.223; 14.AP.244.240; 14.AP.244.244; 14.AP.244.243; 14.AP.244.247; 14.AP.247.157; 14.AP.247.158; 14.AP.247.196; 14.AP.247.223; 14.AP.247.240; 14.AP.247.244; 14.AP.247.243; 14.AP.247.247;

Prodrugs of 14.AZ

14.AZ.4.157; 14.AZ.4.158; 14.AZ.4.196; 14.AZ.4.223; 14.AZ.4.240; 14.AZ.4.244; 14.AZ.4.243; 14.AZ.4.247; 14.AZ.5.157; 14.AZ.5.158; 14.AZ.5.196; 14.AZ.5.223; 14.AZ.5.240; 14.AZ.5.244; 14.AZ.5.243; 14.AZ.5.247; 14.AZ.7.157; 14.AZ.7.158; 14.AZ.7.196; 14.AZ.7.223; 14.AZ.7.240; 14.AZ.7.244; 14.AZ.7.243; 14.AZ.7.247; 14.AZ.15.157; 14.AZ.15.158; 14.AZ.15.196; 14.AZ.15.223; 14.AZ.15.240; 14.AZ.15.244; 14.AZ.15.243; 14.AZ.15.247; 14.AZ.16.157; 14.AZ.16.158; 14.AZ.16.196; 14.AZ.16.223; 14.AZ.16.240; 14.AZ.16.244; 14.AZ.16.243; 14.AZ.16.247; 14.AZ.18.157; 14.AZ.18.158; 14.AZ.18.196; 14.AZ.18.223; 14.AZ.18.240; 14.AZ.18.244; 14.AZ.18.243; 14.AZ.18.247; 14.AZ.26.157; 14.AZ.26.158; 14.AZ.26.196; 14.AZ.26.223; 14.AZ.26.240; 14.AZ.26.244; 14.AZ.26.243; 14.AZ.26.247; 14.AZ.27.157; 14.AZ.27.158; 14.AZ.27.196; 14.AZ.27.223; 14.AZ.27.240; 14.AZ.27.244; 14.AZ.27.243; 14.AZ.27.247; 14.AZ.29.157; 14.AZ.29.158; 14.AZ.29.196; 14.AZ.29.223; 14.AZ.29.240; 14.AZ.29.244; 14.AZ.29.243; 14.AZ.29.247; 14.AZ.54.157; 14.AZ.54.158; 14.AZ.54.196; 14.AZ.54.223; 14.AZ.54.240; 14.AZ.54.244; 14.AZ.54.243; 14.AZ.54.247; 14.AZ.55.157; 14.AZ.55.158; 14.AZ.55.196; 14.AZ.55.223; 14.AZ.55.240; 14.AZ.55.244; 14.AZ.55.243; 14.AZ.55.247; 14.AZ.56.157; 14.AZ.56.158; 14.AZ.56.196; 14.AZ.56.223; 14.AZ.56.240; 14.AZ.56.244; 14.AZ.56.243; 14.AZ.56.247; 14.AZ.157.157; 14.AZ.157.158; 14.AZ.157.196; 14.AZ.157.223; 14.AZ.157.240; 14.AZ.157.244; 14.AZ.157.243; 14.AZ.157.247; 14.AZ.196.157; 14.AZ.196.158; 14.AZ.196.196; 14.AZ.196.223; 14.AZ.196.240; 14.AZ.196.244; 14.AZ.196.243; 14.AZ.196.247; 14.AZ.223.157; 14.AZ.223.158; 14.AZ.223.196; 14.AZ.223.223; 14.AZ.223.240; 14.AZ.223.244; 14.AZ.223.243; 14.AZ.223.247; 14.AZ.240.157; 14.AZ.240.158; 14.AZ.240.196; 14.AZ.240.223; 14.AZ.240.240; 14.AZ.240.244; 14.AZ.240.243; 14.AZ.240.247; 14.AZ.244.157; 14.AZ.244.158; 14.AZ.244.196; 14.AZ.244.223; 14.AZ.244.240; 14.AZ.244.244; 14.AZ.244.243; 14.AZ.244.247; 14.AZ.247.157; 14.AZ.247.158; 14.AZ.247.196; 14.AZ.247.223; 14.AZ.247.240; 14.AZ.247.244; 14.AZ.247.243; 14.AZ.247.247;

Prodrugs of 14.BF

14.BF.4.157; 14.BF.4.158; 14.BF.4.196; 14.BF.4.223; 14.BF.4.240; 14.BF.4.244; 14.BF.4.243; 14.BF.4.247; 14.BF.5.157; 14.BF.5.158; 14.BF.5.196; 14.BF.5.223;

14.BF.5.240; 14.BF.5.244; 14.BF.5.243; 14.BF.5.247; 14.BF.7.157; 14.BF.7.158; 14.BF.7.196; 14.BF.7.223; 14.BF.7.240; 14.BF.7.244; 14.BF.7.243; 14.BF.7.247; 14.BF.15.157; 14.BF.15.158; 14.BF.15.196; 14.BF.15.223; 14.BF.15.240; 14.BF.15.244; 14.BF.15.243; 14.BF.15.247; 14.BF.16.157; 14.BF.16.158; 14.BF.16.196; 14.BF.16.223; 14.BF.16.240; 14.BF.16.244; 14.BF.16.243; 14.BF.16.247; 14.BF.18.157; 14.BF.18.158; 14.BF.18.196; 14.BF.18.223; 14.BF.18.240; 14.BF.18.244; 14.BF.18.243; 14.BF.18.247; 14.BF.26.157; 14.BF.26.158; 14.BF.26.196; 14.BF.26.223; 14.BF.26.240; 14.BF.26.244; 14.BF.26.243; 14.BF.26.247; 14.BF.27.157; 14.BF.27.158; 14.BF.27.196; 14.BF.27.223; 14.BF.27.240; 14.BF.27.244; 14.BF.27.243; 14.BF.27.247; 14.BF.29.157; 14.BF.29.158; 14.BF.29.196; 14.BF.29.223; 14.BF.29.240; 14.BF.29.244; 14.BF.29.243; 14.BF.29.247; 14.BF.54.157; 14.BF.54.158; 14.BF.54.196; 14.BF.54.223; 14.BF.54.240; 14.BF.54.244; 14.BF.54.243; 14.BF.54.247; 14.BF.55.157; 14.BF.55.158; 14.BF.55.196; 14.BF.55.223; 14.BF.55.240; 14.BF.55.244; 14.BF.55.243; 14.BF.55.247; 14.BF.56.157; 14.BF.56.158; 14.BF.56.196; 14.BF.56.223; 14.BF.56.240; 14.BF.56.244; 14.BF.56.243; 14.BF.56.247; 14.BF.157.157; 14.BF.157.158; 14.BF.157.196; 14.BF.157.223; 14.BF.157.240; 14.BF.157.244; 14.BF.157.243; 14.BF.157.247; 14.BF.196.157; 14.BF.196.158; 14.BF.196.196; 14.BF.196.223; 14.BF.196.240; 14.BF.196.244; 14.BF.196.243; 14.BF.196.247; 14.BF.223.157; 14.BF.223.158; 14.BF.223.196; 14.BF.223.223; 14.BF.223.240; 14.BF.223.244; 14.BF.223.243; 14.BF.223.247; 14.BF.240.157; 14.BF.240.158; 14.BF.240.196; 14.BF.240.223; 14.BF.240.240; 14.BF.240.244; 14.BF.240.243; 14.BF.240.247; 14.BF.244.157; 14.BF.244.158; 14.BF.244.196; 14.BF.244.223; 14.BF.244.240; 14.BF.244.244; 14.BF.244.243; 14.BF.244.247; 14.BF.247.157; 14.BF.247.158; 14.BF.247.196; 14.BF.247.223; 14.BF.247.240; 14.BF.247.244; 14.BF.247.243; 14.BF.247.247;

Prodrugs of 14.CI

14.CI.4.157; 14.CI.4.158; 14.CI.4.196; 14.CI.4.223; 14.CI.4.240; 14.CI.4.244; 14.CI.4.243; 14.CI.4.247; 14.CI.5.157; 14.CI.5.158; 14.CI.5.196; 14.CI.5.223; 14.CI.5.240; 14.CI.5.244; 14.CI.5.243; 14.CI.5.247; 14.CI.7.157; 14.CI.7.158; 14.CI.7.196; 14.CI.7.223; 14.CI.7.240; 14.CI.7.244; 14.CI.7.243; 14.CI.7.247; 14.CI.15.157; 14.CI.15.158; 14.CI.15.196; 14.CI.15.223; 14.CI.15.240; 14.CI.15.244; 14.CI.15.243; 14.CI.15.247; 14.CI.16.157; 14.CI.16.158; 14.CI.16.196; 14.CI.16.223; 14.CI.16.240; 14.CI.16.244; 14.CI.16.243; 14.CI.16.247; 14.CI.18.157; 14.CI.18.158; 14.CI.18.196; 14.CI.18.223; 14.CI.18.240; 14.CI.18.244; 14.CI.18.243; 14.CI.18.247; 14.CI.26.157; 14.CI.26.158; 14.CI.26.196; 14.CI.26.223; 14.CI.26.240; 14.CI.26.244; 14.CI.26.243; 14.CI.26.247; 14.CI.27.157; 14.CI.27.158; 14.CI.27.196; 14.CI.27.223; 14.CI.27.240; 14.CI.27.244; 14.CI.27.243; 14.CI.27.247; 14.CI.29.157; 14.CI.29.158; 14.CI.29.196; 14.CI.29.223; 14.CI.29.240; 14.CI.29.244; 14.CI.29.243; 14.CI.29.247; 14.CI.54.157; 14.CI.54.158; 14.CI.54.196; 14.CI.54.223; 14.CI.54.240; 14.CI.54.244; 14.CI.54.243; 14.CI.54.247; 14.CI.55.157; 14.CI.55.158; 14.CI.55.196; 14.CI.55.223; 14.CI.55.240; 14.CI.55.244; 14.CI.55.243; 14.CI.55.247; 14.CI.56.157; 14.CI.56.158; 14.CI.56.196; 14.CI.56.223; 14.CI.56.240; 14.CI.56.244; 14.CI.56.243; 14.CI.56.247; 14.CI.157.157; 14.CI.157.158; 14.CI.157.196; 14.CI.157.223; 14.CI.157.240; 14.CI.157.244; 14.CI.157.243; 14.CI.157.247; 14.CI.196.157; 14.CI.196.158; 14.CI.196.196; 14.CI.196.223; 14.CI.196.240; 14.CI.196.244; 14.CI.196.243; 14.CI.196.247; 14.CI.223.157; 14.CI.223.158; 14.CI.223.196; 14.CI.223.223; 14.CI.223.240; 14.CI.223.244; 14.CI.223.243; 14.CI.223.247; 14.CI.240.157; 14.CI.240.158; 14.CI.240.196; 14.CI.240.223; 14.CI.240.240; 14.CI.240.244; 14.CI.240.243; 14.CI.240.247; 14.CI.244.157; 14.CI.244.158; 14.CI.244.196; 14.CI.244.223; 14.CI.244.240; 14.CI.244.244;

14.CI.244.243; 14.CI.244.247; 14.CI.247.157; 14.CI.247.158; 14.CI.247.196; 14.CI.247.223; 14.CI.247.240; 14.CI.247.244; 14.CI.247.243; 14.CI.247.247;

Prodrugs of 14.CO

14.CO.4.157; 14.CO.4.158; 14.CO.4.196; 14.CO.4.223; 14.CO.4.240; 14.CO.4.244; 14.CO.4.243; 14.CO.4.247; 14.CO.5.157; 14.CO.5.158; 14.CO.5.196; 14.CO.5.223; 14.CO.5.240; 14.CO.5.244; 14.CO.5.243; 14.CO.5.247; 14.CO.7.157; 14.CO.7.158; 14.CO.7.196; 14.CO.7.223; 14.CO.7.240; 14.CO.7.244; 14.CO.7.243; 14.CO.7.247; 14.CO.15.157; 14.CO.15.158; 14.CO.15.196; 14.CO.15.223; 14.CO.15.240; 14.CO.15.244; 14.CO.15.243; 14.CO.15.247; 14.CO.16.157; 14.CO.16.158; 14.CO.16.196; 14.CO.16.223; 14.CO.16.240; 14.CO.16.244; 14.CO.16.243; 14.CO.16.247; 14.CO.18.157; 14.CO.18.158; 14.CO.18.196; 14.CO.18.223; 14.CO.18.240; 14.CO.18.244; 14.CO.18.243; 14.CO.18.247; 14.CO.26.157; 14.CO.26.158; 14.CO.26.196; 14.CO.26.223; 14.CO.26.240; 14.CO.26.244; 14.CO.26.243; 14.CO.26.247; 14.CO.27.157; 14.CO.27.158; 14.CO.27.196; 14.CO.27.223; 14.CO.27.240; 14.CO.27.244; 14.CO.27.243; 14.CO.27.247; 14.CO.29.157; 14.CO.29.158; 14.CO.29.196; 14.CO.29.223; 14.CO.29.240; 14.CO.29.244; 14.CO.29.243; 14.CO.29.247; 14.CO.54.157; 14.CO.54.158; 14.CO.54.196; 14.CO.54.223; 14.CO.54.240; 14.CO.54.244; 14.CO.54.243; 14.CO.54.247; 14.CO.55.157; 14.CO.55.158; 14.CO.55.196; 14.CO.55.223; 14.CO.55.240; 14.CO.55.244; 14.CO.55.243; 14.CO.55.247; 14.CO.56.157; 14.CO.56.158; 14.CO.56.196; 14.CO.56.223; 14.CO.56.240; 14.CO.56.244; 14.CO.56.243; 14.CO.56.247; 14.CO.157.157; 14.CO.157.158; 14.CO.157.196; 14.CO.157.223; 14.CO.157.240; 14.CO.157.244; 14.CO.157.243; 14.CO.157.247; 14.CO.196.157; 14.CO.196.158; 14.CO.196.196; 14.CO.196.223; 14.CO.196.240; 14.CO.196.244; 14.CO.196.243; 14.CO.196.247; 14.CO.223.157; 14.CO.223.158; 14.CO.223.196; 14.CO.223.223; 14.CO.223.240; 14.CO.223.244; 14.CO.223.243; 14.CO.223.247; 14.CO.240.157; 14.CO.240.158; 14.CO.240.196; 14.CO.240.223; 14.CO.240.240; 14.CO.240.244; 14.CO.240.243; 14.CO.240.247; 14.CO.244.157; 14.CO.244.158; 14.CO.244.196; 14.CO.244.223; 14.CO.244.240; 14.CO.244.244; 14.CO.244.243; 14.CO.244.247; 14.CO.4.157; 14.CO.4.158; 14.CO.4.196; 14.CO.4.223; 14.CO.4.240; 14.CO.4.244; 14.CO.4.243; 14.CO.4.247;

Recursive Substituents

Selected substituents within the compounds of the invention are present to a recursive degree. In this context, "recursive substituent" means that a substituent may recite another instance of itself. Because of the recursive nature of such substituents, theoretically, a large number of compounds may be present in any given embodiment. For example, R^x contains a R^y substituent. R^y can be R^2, which in turn can be R^3. If R^3 is selected to be R^{3c}, then a second instance of R^x can be selected. One of ordinary skill in the art of medicinal chemistry understands that the total number of such substituents is reasonably limited by the desired properties of the compound intended. Such properties include, by of example and not limitation, physical properties such as molecular weight, solubility or log P, application properties such as activity against the intended target, and practical properties such as ease of synthesis.

By way of example and not limitation, W^3, R^y and R^3 are all recursive substituents in certain embodiments. Typically, each of these may independently occur 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0, times in a given embodiment. More typically, each of these may independently occur 12 or fewer times in a given embodiment. More typically yet, W^3 will occur 0 to 8 times, R^y will occur 0 to 6 times and R^3 will occur 0 to 10 times in a given embodiment. Even more typically, W^3 will occur 0 to 6 times, R^y will occur 0 to 4 times and R^3 will occur 0 to 8 times in a given embodiment.

Recursive substituents are an intended aspect of the invention. One of ordinary skill in the art of medicinal chemistry understands the versatility of such substituents. To the degree that recursive substituents are present in an embodiment of the invention, the total number will be determined as set forth above.

Protecting Groups

In the context of the present invention, embodiments of protecting groups include prodrug moieties and chemical protecting groups.

Protecting groups are available, commonly known and used, and are optionally used to prevent side reactions with the protected group during synthetic procedures, i.e. routes or methods to prepare the compounds of the invention. For the most part the decision as to which groups to protect, when to do so, and the nature of the chemical protecting group "PRT" will be dependent upon the chemistry of the reaction to be protected against (e.g.,

acidic, basic, oxidative, reductive or other conditions) and the intended direction of the synthesis. The PRT groups do not need to be, and generally are not, the same if the compound is substituted with multiple PRT. In general, PRT will be used to protect functional groups such as carboxyl, hydroxyl or amino groups and to thus prevent side reactions or to otherwise facilitate the synthetic efficiency. The order of deprotection to yield free, deprotected groups is dependent upon the intended direction of the synthesis and the reaction conditions to be encountered, and may occur in any order as determined by the artisan.

Various functional groups of the compounds of the invention may be protection. For example, protecting groups for -OH groups (whether hydroxyl, carboxylic acid, phosphonic acid, or other functions) are embodiments of "ether- or ester-forming groups". Ether- or ester-forming groups are capable of functioning as chemical protecting groups in the synthetic schemes set forth herein. However, some hydroxyl and thio protecting groups are neither ether- nor ester-forming groups, as will be understood by those skilled in the art, and are included with amides, discussed below.

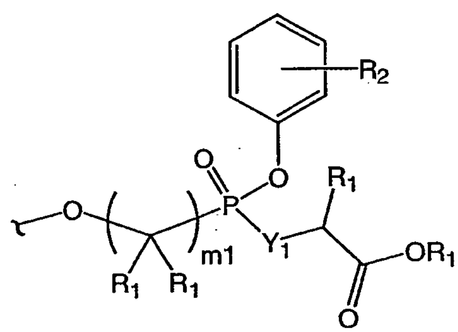
A very large number of hydroxyl protecting groups and amide-forming groups and corresponding chemical cleavage reactions are described in "Protective Groups in Organic Chemistry", Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991, ISBN 0-471-62301-6) ("Greene"). See also Kocienski, Philip J.; "Protecting Groups" (Georg Thieme Verlag Stuttgart, New York, 1994), which is incorporated by reference in its entirety herein. In particular Chapter 1, Protecting Groups: An Overview, pages 1-20, Chapter 2, Hydroxyl Protecting Groups, pages 21-94, Chapter 3, Diol Protecting Groups, pages 95-117, Chapter 4, Carboxyl Protecting Groups, pages 118-154, Chapter 5, Carbonyl Protecting Groups, pages 155-184. For protecting groups for carboxylic acid, phosphonic acid, phosphonate, sulfonic acid and other protecting groups for acids see Greene as set forth below. Such groups include by way of example and not limitation, esters, amides, hydrazides, and the like.

Ether- and Ester-forming protecting groups

Ester-forming groups include: (1) phosphonate ester-forming groups, such as phosphonamidate esters, phosphorothioate esters, phosphonate esters, and phosphon-bis-amidates; (2) carboxyl ester-forming groups, and (3) sulphur ester-forming groups, such as sulphonate, sulfate, and sulfinate.

The phosphonate moieties of the compounds of the invention may or may not be prodrug moieties, i.e. they may or may not be susceptible to hydrolytic or enzymatic cleavage or modification. Certain phosphonate moieties are stable under most or nearly all metabolic conditions. For example, a dialkylphosphonate, where the alkyl groups are two or more carbons, may have appreciable stability *in vivo* due to a slow rate of hydrolysis.

Within the context of phosphonate prodrug moieties, a large number of structurally-diverse prodrugs have been described for phosphonic acids (Freeman and Ross in Progress in Medicinal Chemistry 34: 112-147 (1997) and are included within the scope of the present invention. An exemplary embodiment of a phosphonate ester-forming group is the phenyl carbocycle in substructure A_3 having the formula:

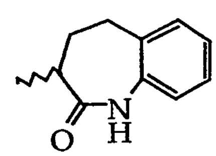


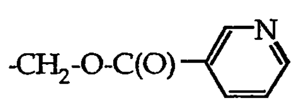
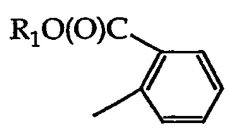
wherein m1 is 1, 2, 3, 4, 5, 6, 7 or 8, and the phenyl carbocycle is substituted with 0 to 3 R_2 groups. Also, in this embodiment, where Y_1 is O, a lactate ester is formed. Alternatively, where Y_1 is $N(R_2)$, $N(OR_2)$ or $N(N(R_2)_2$, then phosphonamidate esters result. R_1 may be H or C_1–C_{12} alkyl. The corollary exemplary substructure A^3 is included in the invention with Y^1, R^1 and R^2 substituents.

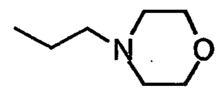
In its ester-forming role, a protecting group typically is bound to any acidic group such as, by way of example and not limitation, a $-CO_2H$ or $-C(S)OH$ group, thereby resulting in $-CO_2R^x$ where R^x is defined herein. Also, R^x for example includes the enumerated ester groups of WO 95/07920.

Examples of protecting groups include:

C_3–C_{12} heterocycle (described above) or aryl. These aromatic groups optionally are polycyclic or monocyclic. Examples include phenyl, spiryl, 2- and 3-pyrrolyl, 2- and 3-thienyl, 2- and 4-imidazolyl, 2-, 4- and 5-oxazolyl, 3- and 4-isoxazolyl, 2-, 4- and 5-thiazolyl, 3-, 4- and 5-isothiazolyl, 3- and 4-pyrazolyl, 1-, 2-, 3- and 4-pyridinyl, and 1-, 2-, 4- and 5-pyrimidinyl,

C_3-C_{12} heterocycle or aryl substituted with halo, R^1, R^1-O-C_1-C_{12} alkylene, C_1-C_{12} alkoxy, CN, NO_2, OH, carboxy, carboxyester, thiol, thioester, C_1-C_{12} haloalkyl (1-6 halogen atoms), C_2-C_{12} alkenyl or C_2-C_{12} alkynyl. Such groups include 2-, 3- and 4-alkoxyphenyl (C_1-C_{12} alkyl), 2-, 3- and 4-methoxyphenyl, 2-, 3- and 4-ethoxyphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-diethoxyphenyl, 2- and 3-carboethoxy-4-hydroxyphenyl, 2- and 3-ethoxy-4-hydroxyphenyl, 2- and 3-ethoxy-5-hydroxyphenyl, 2- and 3-ethoxy-6-hydroxyphenyl, 2-, 3- and 4-O-acetylphenyl, 2-, 3- and 4-dimethylaminophenyl, 2-, 3- and 4-methylmercaptophenyl, 2-, 3- and 4-halophenyl (including 2-, 3- and 4-fluorophenyl and 2-, 3- and 4-chlorophenyl), 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dimethylphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-biscarboxyethylphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dimethoxyphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dihalophenyl (including 2,4-difluorophenyl and 3,5-difluorophenyl), 2-, 3- and 4-haloalkylphenyl (1 to 5 halogen atoms, C_1-C_{12} alkyl including 4-trifluoromethylphenyl), 2-, 3- and 4-cyanophenyl, 2-, 3- and 4-nitrophenyl, 2-, 3- and 4-haloalkylbenzyl (1 to 5 halogen atoms, C_1-C_{12} alkyl including 4-trifluoromethylbenzyl and 2-, 3- and 4-trichloromethylphenyl and 2-, 3- and 4-trichloromethylphenyl), 4-N-methylpiperidinyl, 3-N-methylpiperidinyl, 1-ethylpiperazinyl, benzyl, alkylsalicylphenyl (C_1-C_4 alkyl, including 2-, 3- and 4-ethylsalicylphenyl), 2-,3- and 4-acetylphenyl, 1,8-dihydroxynaphthyl (-$C_{10}H_6$-OH) and aryloxy ethyl [C_6-C_9 aryl (including phenoxy ethyl)], 2,2'-dihydroxybiphenyl, 2-, 3- and 4-N,N-dialkylaminophenol, -$C_6H_4CH_2$-$N(CH_3)_2$, trimethoxybenzyl, triethoxybenzyl, 2-alkyl pyridinyl (C_{1-4} alkyl);  ;

 ;  ; C_4 - C_8 esters of 2-carboxyphenyl; and C_1-C_4 alkylene-C_3-C_6 aryl (including benzyl, -CH_2-pyrrolyl, -CH_2-thienyl, -CH_2-imidazolyl, -CH_2-oxazolyl, -CH_2-isoxazolyl, -CH_2-thiazolyl, -CH_2-isothiazolyl, -CH_2-pyrazolyl, -CH_2-pyridinyl and -CH_2-pyrimidinyl) substituted in the aryl moiety by 3 to 5 halogen atoms or 1 to 2 atoms or groups selected from halogen, C_1-C_{12} alkoxy (including methoxy and ethoxy), cyano, nitro, OH, C_1-C_{12} haloalkyl (1 to 6 halogen atoms; including -CH_2CCl_3), C_1-C_{12} alkyl (including methyl and ethyl), C_2-C_{12} alkenyl or C_2-C_{12} alkynyl; alkoxy ethyl [C_1-C_6

alkyl including $-CH_2-CH_2-O-CH_3$ (methoxy ethyl)]; alkyl substituted by any of the groups set forth above for aryl, in particular OH or by 1 to 3 halo atoms (including $-CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, $-(CH_2)_3CH_3$, $-(CH_2)_4CH_3$, $-(CH_2)_5CH_3$, CH_2CH_2F, $-CH_2CH_2Cl$, $-CH_2CF_3$, and $-CH_2CCl_3$);  ; -N-2-propylmorpholino, 2,3-dihydro-6-hydroxyindene, sesamol, catechol monoester, $-CH_2-C(O)-N(R^1)_2$, $-CH_2-S(O)(R^1)$, $-CH_2-S(O)_2(R^1)$, $-CH_2-CH(OC(O)CH_2R^1)-CH_2(OC(O)CH_2R^1)$, cholesteryl, enolpyruvate ($HOOC-C(=CH_2)-$), glycerol;

a 5 or 6 carbon monosaccharide, disaccharide or oligosaccharide (3 to 9 monosaccharide residues);

triglycerides such as α-D-β-diglycerides (wherein the fatty acids composing glyceride lipids generally are naturally occurring saturated or unsaturated C_{6-26}, C_{6-18} or C_{6-10} fatty acids such as linoleic, lauric, myristic, palmitic, stearic, oleic, palmitoleic, linolenic and the like fatty acids) linked to acyl of the parental compounds herein through a glyceryl oxygen of the triglyceride;

phospholipids linked to the carboxyl group through the phosphate of the phospholipid;

phthalidyl (shown in Fig. 1 of Clayton et al., *Antimicrob. Agents Chemo.* (1974) 5(6):670-671;

cyclic carbonates such as (5-R_d-2-oxo-1,3-dioxolen-4-yl) methyl esters (Sakamoto et al., *Chem. Pharm. Bull.* (1984) 32(6)2241-2248) where R_d is R_1, R_4 or aryl; and


;

The hydroxyl groups of the compounds of this invention optionally are substituted with one of groups III, IV or V disclosed in WO 94/21604, or with isopropyl.

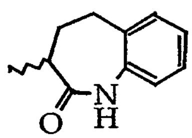
As further embodiments, Table A lists examples of protecting group ester moieties that for example can be bonded via oxygen to $-C(O)O-$ and $-P(O)(O-)_2$ groups. Several amidates also are shown, which are bound directly to $-C(O)-$ or $-P(O)_2$. Esters of structures 1-5, 8-10 and 16, 17, 19-22 are synthesized by reacting the compound herein having a free hydroxyl with the corresponding halide (chloride or acyl chloride and the like) and N ,N-dicyclohexyl-N-morpholine carboxamidine (or another base such as DBU, triethylamine, $CsCO_3$, N,N-

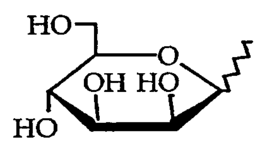
dimethylaniline and the like) in DMF (or other solvent such as acetonitrile or N-methylpyrrolidone). When the compound to be protected is a phosphonate, the esters of structures 5-7, 11, 12, 21, and 23-26 are synthesized by reaction of the alcohol or alkoxide salt (or the corresponding amines in the case of compounds such as 13, 14 and 15) with the monochlorophosphonate or dichlorophosphonate (or another activated phosphonate).

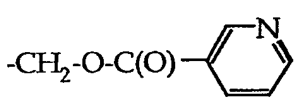
TABLE A

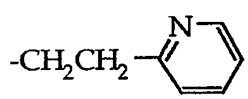
1. $-CH_2-C(O)-N(R_1)_2$ *	10. $-CH_2-O-C(O)-C(CH_3)_3$
2. $-CH_2-S(O)(R_1)$	11. $-CH_2-CCl_3$
3. $-CH_2-S(O)_2(R_1)$	12. $-C_6H_5$
4. $-CH_2-O-C(O)-CH_2-C_6H_5$	13. $-NH-CH_2-C(O)O-CH_2CH_3$
5. 3-cholesteryl	14. $-N(CH_3)-CH_2-C(O)O-CH_2CH_3$
6. 3-pyridyl	15. $-NHR_1$
7. N-ethylmorpholino	16. $-CH_2-O-C(O)-C_{10}H_{15}$
8. $-CH_2-O-C(O)-C_6H_5$	17. $-CH_2-O-C(O)-CH(CH_3)_2$
9. $-CH_2-O-C(O)-CH_2CH_3$	18. $-CH_2-C\#H(OC(O)CH_2R_1)-CH_2-(OC(O)CH_2R_1)$*

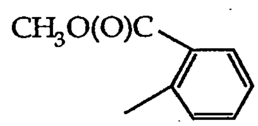
19. 

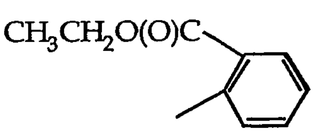
20. 

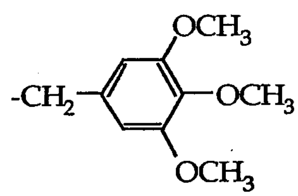
21. 

22. 

23. 

24. 

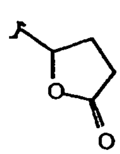
25. 

26. 

\# - chiral center is (R), (S) or racemate.

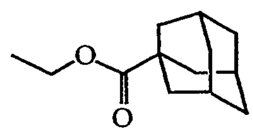
Other esters that are suitable for use herein are described in EP 632048.

Protecting groups also includes "double ester" forming profunctionalities such as



$-CH_2OC(O)OCH_3$, $-CH_2SCOCH_3$, $-CH_2OCON(CH_3)_2$, or alkyl- or aryl-acyloxyalkyl groups of the structure $-CH(R^1 \text{ or } W^5)O((CO)R^{37})$ or

$-CH(R^1$ or $W^5)((CO)OR^{38})$ (linked to oxygen of the acidic group) wherein R^{37} and R^{38} are alkyl, aryl, or alkylaryl groups (see U.S. Patent No. 4,968,788). Frequently R^{37} and R^{38} are bulky groups such as branched alkyl, ortho-substituted aryl, meta-substituted aryl, or combinations thereof, including normal, secondary, iso- and tertiary alkyls of 1-6 carbon atoms. An example is the pivaloyloxymethyl group. These are of particular use with prodrugs for oral administration. Examples of such useful protecting groups are alkylacyloxymethyl esters and their derivatives, including -

$CH(CH_2CH_2OCH_3)OC(O)C(CH_3)_3$,  ;

$-CH_2OC(O)C_{10}H_{15}$, $-CH_2OC(O)C(CH_3)_3$, $-CH(CH_2OCH_3)OC(O)C(CH_3)_3$, $-CH(CH(CH_3)_2)OC(O)C(CH_3)_3$, $-CH_2OC(O)CH_2CH(CH_3)_2$, $-CH_2OC(O)C_6H_{11}$, $-CH_2OC(O)C_6H_5$, $-CH_2OC(O)C_{10}H_{15}$, $-CH_2OC(O)CH_2CH_3$, $-CH_2OC(O)CH(CH_3)_2$, $-CH_2OC(O)C(CH_3)_3$ and $-CH_2OC(O)CH_2C_6H_5$.

For prodrug purposes, the ester typically chosen is one heretofore used for antibiotic drugs, in particular the cyclic carbonates, double esters, or the phthalidyl, aryl or alkyl esters.

In some embodiments the protected acidic group is an ester of the acidic group and is the residue of a hydroxyl-containing functionality. In other embodiments, an amino compound is used to protect the acid functionality. The residues of suitable hydroxyl or amino-containing functionalities are set forth above or are found in WO 95/07920. Of particular interest are the residues of amino acids, amino acid esters, polypeptides, or aryl alcohols. Typical amino acid, polypeptide and carboxyl-esterified amino acid residues are described on pages 11-18 and related text of WO 95/07920 as groups L1 or L2. WO 95/07920 expressly teaches the amidates of phosphonic acids, but it will be understood that such amidates are formed with any of the acid groups set forth herein and the amino acid residues set forth in WO 95/07920.

Typical esters for protecting acidic functionalities are also described in WO 95/07920, again understanding that the same esters can be formed with the acidic groups herein as with the phosphonate of the '920 publication. Typical ester groups are defined at least on WO 95/07920 pages 89-93 (under R^{31} or R^{35}), the table on page 105, and pages 21-23 (as R). Of particular interest are esters of unsubstituted aryl such as phenyl or arylalkyl such benzyl, or hydroxy-, halo-, alkoxy-, carboxy- and/or alkylestercarboxy-substituted aryl or alkylaryl,

especially phenyl, ortho-ethoxyphenyl, or C_1-C_4 alkylestercarboxyphenyl (salicylate C_1-C_{12} alkylesters).

The protected acidic groups, particularly when using the esters or amides of WO 95/07920, are useful as prodrugs for oral administration. However, it is not essential that the acidic group be protected in order for the compounds of this invention to be effectively administered by the oral route. When the compounds of the invention having protected groups, in particular amino acid amidates or substituted and unsubstituted aryl esters are administered systemically or orally they are capable of hydrolytic cleavage *in vivo* to yield the free acid.

One or more of the acidic hydroxyls are protected. If more than one acidic hydroxyl is protected then the same or a different protecting group is employed, e.g., the esters may be different or the same, or a mixed amidate and ester may be used.

Typical hydroxy protecting groups described in Greene (pages 14-118) include substituted methyl and alkyl ethers, substituted benzyl ethers, silyl ethers, esters including sulfonic acid esters, and carbonates. For example:

- Ethers (methyl, *t*-butyl, allyl);
- Substituted Methyl Ethers (Methoxymethyl, Methylthiomethyl, *t*-Butylthiomethyl, (Phenyldimethylsilyl)methoxymethyl, Benzyloxymethyl, *p*-Methoxybenzyloxymethyl, (4-Methoxyphenoxy)methyl, Guaiacolmethyl, *t*-Butoxymethyl, 4-Pentenyloxymethyl, Siloxymethyl, 2-Methoxyethoxymethyl, 2,2,2-Trichloroethoxymethyl, Bis(2-chloroethoxy)methyl, 2-(Trimethylsilyl)ethoxymethyl, Tetrahydropyranyl, 3-Bromotetrahydropyranyl, Tetrahydropthiopyranyl, 1-Methoxycyclohexyl, 4-Methoxytetrahydropyranyl, 4-Methoxytetrahydrothiopyranyl, 4-Methoxytetrahydropthiopyranyl *S,S*-Dioxido, 1-[(2-Chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl, 1,4-Dioxan-2-yl, Tetrahydrofuranyl, Tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a-Octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl));
- Substituted Ethyl Ethers (1-Ethoxyethyl, 1-(2-Chloroethoxy)ethyl, 1-Methyl-1-methoxyethyl, 1-Methyl-1-benzyloxyethyl, 1-Methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-Trichloroethyl, 2-Trimethylsilylethyl, 2-(Phenylselenyl)ethyl,
- *p*-Chlorophenyl, *p*-Methoxyphenyl, 2,4-Dinitrophenyl, Benzyl);
- Substituted Benzyl Ethers (*p*-Methoxybenzyl, 3,4-Dimethoxybenzyl, *o*-Nitrobenzyl, *p*-Nitrobenzyl, *p*-Halobenzyl, 2,6-Dichlorobenzyl, *p*-Cyanobenzyl, *p*-Phenylbenzyl, 2- and

4-Picolyl, 3-Methyl-2-picolyl *N*-Oxido, Diphenylmethyl, *p,p'*-Dinitrobenzhydryl, 5-Dibenzosuberyl, Triphenylmethyl, α-Naphthyldiphenylmethyl, *p*-methoxyphenyldiphenylmethyl, Di(*p*-methoxyphenyl)phenylmethyl, Tri(*p*-methoxyphenyl)methyl, 4-(4'-Bromophenacyloxy)phenyldiphenylmethyl, 4,4',4"-Tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4"-Tris(levulinoyloxyphenyl)methyl, 4,4',4"-Tris(benzoyloxyphenyl)methyl, 3-(Imidazol-1-ylmethyl)bis(4',4"-dimethoxyphenyl)methyl, 1,1-Bis(4-methoxyphenyl)-1'-pyrenylmethyl, 9-Anthryl, 9-(9-Phenyl)xanthenyl, 9-(9-Phenyl-10-oxo)anthryl, 1,3-Benzodithiolan-2-yl, Benzisothiazolyl *S,S*-Dioxido);

- Silyl Ethers (Trimethylsilyl, Triethylsilyl, Triisopropylsilyl, Dimethylisopropylsilyl, Diethylisopropylsilyl, Dimethylthexylsilyl, *t*-Butyldimethylsilyl, *t*-Butyldiphenylsilyl, Tribenzylsilyl, Tri-*p*-xylylsilyl, Triphenylsilyl, Diphenylmethylsilyl, *t*-Butylmethoxyphenylsilyl);
- Esters (Formate, Benzoylformate, Acetate, Choroacetate, Dichloroacetate, Trichloroacetate, Trifluoroacetate, Methoxyacetate, Triphenylmethoxyacetate, Phenoxyacetate, *p*-Chlorophenoxyacetate, *p*-poly-Phenylacetate, 3-Phenylpropionate, 4-Oxopentanoate (Levulinate), 4,4-(Ethylenedithio)pentanoate, Pivaloate, Adamantoate, Crotonate, 4-Methoxycrotonate, Benzoate, *p*-Phenylbenzoate, 2,4,6-Trimethylbenzoate (Mesitoate));
- Carbonates (Methyl, 9-Fluorenylmethyl, Ethyl, 2,2,2-Trichloroethyl, 2-(Trimethylsilyl)ethyl, 2-(Phenylsulfonyl)ethyl, 2-(Triphenylphosphonio)ethyl, Isobutyl, Vinyl, Allyl, *p*-Nitrophenyl, Benzyl, *p*-Methoxybenzyl, 3,4-Dimethoxybenzyl, *o*-Nitrobenzyl, *p*-Nitrobenzyl, *S*-Benzyl Thiocarbonate, 4-Ethoxy-1-naphthyl, Methyl Dithiocarbonate);
- Groups With Assisted Cleavage (2-Iodobenzoate, 4-Azidobutyrate, 4-Nitro-4-methylpentanoate, *o*-(Dibromomethyl)benzoate, 2-Formylbenzenesulfonate, 2-(Methylthiomethoxy)ethyl Carbonate, 4-(Methylthiomethoxy)butyrate, 2-(Methylthiomethoxymethyl)benzoate); Miscellaneous Esters (2,6-Dichloro-4-methylphenoxyacetate, 2,6-Dichloro-4-(1,1,3,3 tetramethylbutyl)phenoxyacetate, 2,4-Bis(1,1-dimethylpropyl)phenoxyacetate, Chlorodiphenylacetate, Isobutyrate, Monosuccinate, (*E*)-2-Methyl-2-butenoate (Tigloate), *o*-(Methoxycarbonyl)benzoate, *p*-poly-Benzoate, α-Naphthoate, Nitrate, Alkyl *N,N,N',N'*-Tetramethylphosphorodiamidate,

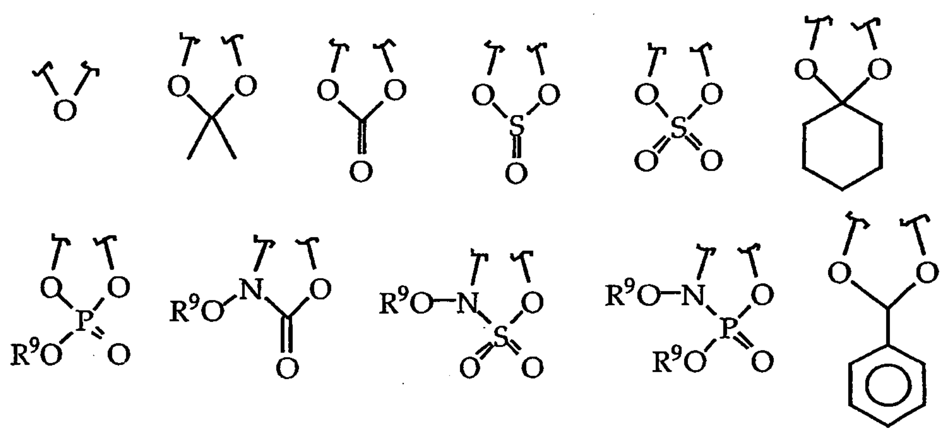
N-Phenylcarbamate, Borate, Dimethylphosphinothioyl, 2,4-Dinitrophenylsulfenate); and

- Sulfonates (Sulfate, Methanesulfonate (Mesylate), Benzylsulfonate, Tosylate).

Typical 1,2-diol protecting groups (thus, generally where two OH groups are taken together with the protecting functionality) are described in Greene at pages 118-142 and include Cyclic Acetals and Ketals (Methylene, Ethylidene, 1-*t*-Butylethylidene, 1-Phenylethylidene, (4-Methoxyphenyl)ethylidene, 2,2,2-Trichloroethylidene, Acetonide (Isopropylidene), Cyclopentylidene, Cyclohexylidene, Cycloheptylidene, Benzylidene, *p*-Methoxybenzylidene, 2,4-Dimethoxybenzylidene, 3,4-Dimethoxybenzylidene, 2-Nitrobenzylidene); Cyclic Ortho Esters (Methoxymethylene, Ethoxymethylene, Dimethoxymethylene, 1-Methoxyethylidene, 1-Ethoxyethylidine, 1,2-Dimethoxyethylidene, α-Methoxybenzylidene, 1-(*N,N*-Dimethylamino)ethylidene Derivative, α -(*N,N*-Dimethylamino)benzylidene Derivative, 2-Oxacyclopentylidene); Silyl Derivatives (Di-*t*-butylsilylene Group, 1,3-(1,1,3,3-Tetraisopropyldisiloxanylidene), and Tetra-*t*-butoxydisiloxane-1,3-diylidene), Cyclic Carbonates, Cyclic Boronates, Ethyl Boronate and Phenyl Boronate.

More typically, 1,2-diol protecting groups include those shown in Table B, still more typically, epoxides, acetonides, cyclic ketals and aryl acetals.

Table B



wherein R^9 is C_1-C_6 alkyl.

<u>Amino protecting groups</u>

Another set of protecting groups include any of the typical amino protecting groups described by Greene at pages 315-385. They include:

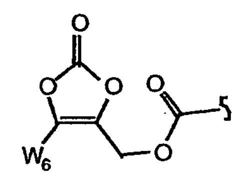
- Carbamates: (methyl and ethyl, 9-fluorenylmethyl, 9(2-sulfo)fluorenylmethyl, 9-(2,7-dibromo)fluorenylmethyl, 2,7-di-*t*-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl, 4-methoxyphenacyl);
- Substituted Ethyl: (2,2,2-trichoroethyl, 2-trimethylsilylethyl, 2-phenylethyl, 1-(1-adamantyl)-1-methylethyl, 1,1-dimethyl-2-haloethyl, 1,1-dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl, 1-methyl-1-(4-biphenylyl)ethyl, 1-(3,5-di-*t*-butylphenyl)-1-methylethyl, 2-(2'- and 4'-pyridyl)ethyl, 2-(*N,N*-dicyclohexylcarboxamido)ethyl, *t*-butyl, 1-adamantyl, vinyl, allyl, 1-isopropylallyl, cinnamyl, 4-nitrocinnamyl, 8-quinolyl, *N*-hydroxypiperidinyl, alkyldithio, benzyl, *p*-methoxybenzyl, *p*-nitrobenzyl, *p*-bromobenzyl, *p*-chlorobenzyl, 2,4-dichlorobenzyl, 4-methylsulfinylbenzyl, 9-anthrylmethyl, diphenylmethyl);
- Groups With Assisted Cleavage: (2-methylthioethyl, 2-methylsulfonylethyl, 2-(*p*-toluenesulfonyl)ethyl, [2-(1,3-dithianyl)]methyl, 4-methylthiophenyl, 2,4-dimethylthiophenyl, 2-phosphonioethyl, 2-triphenylphosphonioisopropyl, 1,1-dimethyl-2-cyanoethyl, *m*-choro-*p*-acyloxybenzyl, *p*-(dihydroxyboryl)benzyl, 5-benzisoxazolylmethyl, 2-(trifluoromethyl)-6-chromonylmethyl);
- Groups Capable of Photolytic Cleavage: (*m*-nitrophenyl, 3,5-dimethoxybenzyl, *o*-nitrobenzyl, 3,4-dimethoxy-6-nitrobenzyl, phenyl(*o*-nitrophenyl)methyl); Urea-Type Derivatives (phenothiazinyl-(10)-carbonyl, *N'*-*p*-toluenesulfonylaminocarbonyl, *N'*-phenylaminothiocarbonyl);
- Miscellaneous Carbamates: (*t*-amyl, *S*-benzyl thiocarbamate, *p*-cyanobenzyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclopropylmethyl, *p*-decyloxybenzyl, diisopropylmethyl, 2,2-dimethoxycarbonylvinyl, *o*-(*N,N*-dimethylcarboxamido)benzyl, 1,1-dimethyl-3-(*N,N*-dimethylcarboxamido)propyl, 1,1-dimethylpropynyl, di(2-pyridyl)methyl, 2-furanylmethyl, 2-Iodoethyl, Isobornyl, Isobutyl, Isonicotinyl, *p*-(*p'*-Methoxyphenylazo)benzyl, 1-methylcyclobutyl, 1-methylcyclohexyl, 1-methyl-1-cyclopropylmethyl, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl, 1-methyl-1-(*p*-phenylazophenyl)ethyl, 1-methyl-1-phenylethyl, 1-methyl-1-(4-pyridyl)ethyl, phenyl, *p*-(phenylazo)benzyl, 2,4,6-tri-*t*-butylphenyl, 4-(trimethylammonium)benzyl, 2,4,6-trimethylbenzyl);
- Amides: (*N*-formyl, *N*-acetyl, *N*-choroacetyl, *N*-trichoroacetyl, *N*-trifluoroacetyl, *N*-phenylacetyl, *N*-3-phenylpropionyl, *N*-picolinoyl, *N*-3-pyridylcarboxamide, *N*-

benzoylphenylalanyl, *N*-benzoyl, *N*-*p*-phenylbenzoyl);

- Amides With Assisted Cleavage: (*N*-*o*-nitrophenylacetyl, *N*-*o*-nitrophenoxyacetyl, *N*-acetoacetyl, (*N'*-dithiobenzyloxycarbonylamino)acetyl, *N*-3-(*p*-hydroxyphenyl)propionyl, *N*-3-(*o*-nitrophenyl)propionyl, *N*-2-methyl-2-(*o*-nitrophenoxy)propionyl, *N*-2-methyl-2-(*o*-phenylazophenoxy)propionyl, *N*-4-chlorobutyryl, *N*-3-methyl-3-nitrobutyryl, *N*-*o*-nitrocinnamoyl, *N*-acetylmethionine, *N*-*o*-nitrobenzoyl, *N*-*o*-(benzoyloxymethyl)benzoyl, 4,5-diphenyl-3-oxazolin-2-one);
- Cyclic Imide Derivatives: (*N*-phthalimide, *N*-dithiasuccinoyl, *N*-2,3-diphenylmaleoyl, *N*-2,5-dimethylpyrrolyl, *N*-1,1,4,4-tetramethyldisilylazacyclopentane adduct, 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3-5-triazacyclohexan-2-one, 1-substituted 3,5-dinitro-4-pyridonyl);
- *N*-Alkyl and *N*-Aryl Amines: (*N*-methyl, *N*-allyl, *N*-[2-(trimethylsilyl)ethoxy]methyl, *N*-3-acetoxypropyl, *N*-(1-isopropyl-4-nitro-2-oxo-3-pyrrolin-3-yl), Quaternary Ammonium Salts, *N*-benzyl, *N*-di(4-methoxyphenyl)methyl, *N*-5-dibenzosuberyl, *N*-triphenylmethyl, *N*-(4-methoxyphenyl)diphenylmethyl, *N*-9-phenylfluorenyl, *N*-2,7-dichloro-9-fluorenylmethylene, *N*-ferrocenylmethyl, *N*-2-picolylamine *N'*-oxide);
- Imine Derivatives: (*N*-1,1-dimethylthiomethylene, *N*-benzylidene, *N*-*p*-methoxybenylidene, *N*-diphenylmethylene, *N*-[(2-pyridyl)mesityl]methylene, *N*,(*N'*,*N'*-dimethylaminomethylene, *N*,*N'*-isopropylidene, *N*-*p*-nitrobenzylidene, *N*-salicylidene, *N*-5-chlorosalicylidene, *N*-(5-chloro-2-hydroxyphenyl)phenylmethylene, *N*-cyclohexylidene);
- Enamine Derivatives: (*N*-(5,5-dimethyl-3-oxo-1-cyclohexenyl));
- *N*-Metal Derivatives (*N*-borane derivatives, *N*-diphenylborinic acid derivatives, *N*-[phenyl(pentacarbonylchromium- or -tungsten)]carbenyl, *N*-copper or *N*-zinc chelate);
- N-N Derivatives: (*N*-nitro, *N*-nitroso, *N*-oxide);
- N-P Derivatives: (*N*-diphenylphosphinyl, *N*-dimethylthiophosphinyl, *N*-diphenylthiophosphinyl, *N*-dialkyl phosphoryl, *N*-dibenzyl phosphoryl, *N*-diphenyl phosphoryl);
- N-Si Derivatives, N-S Derivatives, and N-Sulfenyl Derivatives: (*N*-benzenesulfenyl, *N*-*o*-nitrobenzenesulfenyl, *N*-2,4-dinitrobenzenesulfenyl, *N*-pentachlorobenzenesulfenyl, *N*-2-nitro-4-methoxybenzenesulfenyl, *N*-triphenylmethylsulfenyl, *N*-3-nitropyridinesulfenyl); and *N*-sulfonyl Derivatives (*N*-*p*-toluenesulfonyl, *N*-benzenesulfonyl, *N*-2,3,6-trimethyl-

4-methoxybenzenesulfonyl, *N*-2,4,6-trimethoxybenzenesulfonyl, *N*-2,6-dimethyl-4-methoxybenzenesulfonyl, *N*-pentamethylbenzenesulfonyl, *N*-2,3,5,6,-tetramethyl-4-methoxybenzenesulfonyl, *N*-4-methoxybenzenesulfonyl, *N*-2,4,6-trimethylbenzenesulfonyl, *N*-2,6-dimethoxy-4-methylbenzenesulfonyl, *N*-2,2,5,7,8-pentamethylchroman-6-sulfonyl, *N*-methanesulfonyl, *N*-β-trimethylsilyethanesulfonyl, *N*-9-anthracenesulfonyl, *N*-4-(4',8'-dimethoxynaphthylmethyl)benzenesulfonyl, *N*-benzylsulfonyl, *N*-trifluoromethylsulfonyl, *N*-phenacylsulfonyl).

Protected amino groups include carbamates, amides and amidines, e.g. $-NHC(O)OR^1$, $-NHC(O)R^1$ or $-N{=}CR^1N(R^1)_2$. Another protecting group, also useful as a prodrug for amino or $-NH(R^5)$, is:



See for example Alexander, J. et al (1996) *J. Med. Chem.* 39:480-486.

Amino acid and polypeptide protecting group and conjugates

An amino acid or polypeptide protecting group of a compound of the invention has the structure $R^{15}NHCH(R^{16})C(O)-$, where R^{15} is H, an amino acid or polypeptide residue, or R^5, and R^{16} is defined below.

R^{16} is lower alkyl or lower alkyl (C_1-C_6) substituted with amino, carboxyl, amide, carboxyl ester, hydroxyl, C_6-C_7 aryl, guanidinyl, imidazolyl, indolyl, sulfhydryl, sulfoxide, and/or alkylphosphate. R^{16} also is taken together with the amino acid α-N to form a proline residue ($R^{16} = -CH_2)_3-$). However, R^{16} is generally the side group of a naturally-occurring amino acid such as H, $-CH_3$, $-CH(CH_3)_2$, $-CH_2-CH(CH_3)_2$, $-CHCH_3-CH_2-CH_3$, $-CH_2-C_6H_5$, $-CH_2CH_2-S-CH_3$, $-CH_2OH$, $-CH(OH)-CH_3$, $-CH_2-SH$, $-CH_2-C_6H_4OH$, $-CH_2-CO-NH_2$, $-CH_2-CH_2-CO-NH_2$, $-CH_2-COOH$, $-CH_2-CH_2-COOH$, $-(CH_2)_4-NH_2$ and $-(CH_2)_3-NH-C(NH_2)-NH_2$. R^{16} also includes 1-guanidinoprop-3-yl, benzyl, 4-hydroxybenzyl, imidazol-4-yl, indol-3-yl, methoxyphenyl and ethoxyphenyl.

Another set of protecting groups include the residue of an amino-containing compound, in particular an amino acid, a polypeptide, a protecting group, $-NHSO_2R$,

NHC(O)R, $-N(R)_2$, NH_2 or -NH(R)(H), whereby for example a carboxylic acid is reacted, i.e. coupled, with the amine to form an amide, as in $C(O)NR_2$. A phosphonic acid may be reacted with the amine to form a phosphonamidate, as in $-P(O)(OR)(NR_2)$.

Amino acids have the structure $R^{17}C(O)CH(R^{16})NH$-, where R^{17} is -OH, -OR, an amino acid or a polypeptide residue. Amino acids are low molecular weight compounds, on the order of less than about 1000 MW and which contain at least one amino or imino group and at least one carboxyl group. Generally the amino acids will be found in nature, i.e., can be detected in biological material such as bacteria or other microbes, plants, animals or man. Suitable amino acids typically are alpha amino acids, i.e. compounds characterized by one amino or imino nitrogen atom separated from the carbon atom of one carboxyl group by a single substituted or unsubstituted alpha carbon atom. Of particular interest are hydrophobic residues such as mono-or di-alkyl or aryl amino acids, cycloalkylamino acids and the like. These residues contribute to cell permeability by increasing the partition coefficient of the parental drug. Typically, the residue does not contain a sulfhydryl or guanidino substituent.

Naturally-occurring amino acid residues are those residues found naturally in plants, animals or microbes, especially proteins thereof. Polypeptides most typically will be substantially composed of such naturally-occurring amino acid residues. These amino acids are glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, methionine, glutamic acid, aspartic acid, lysine, hydroxylysine, arginine, histidine, phenylalanine, tyrosine, tryptophan, proline, asparagine, glutamine and hydroxyproline. Additionally, unnatural amino acids, for example, valanine, phenylglycine and homoarginine are also included. Commonly encountered amino acids that are not gene-encoded may also be used in the present invention. All of the amino acids used in the present invention may be either the D- or L- optical isomer. In addition, other peptidomimetics are also useful in the present invention. For a general review, see Spatola, A. F., in *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*, B. Weinstein, eds., Marcel Dekker, New York, p. 267 (1983).

When protecting groups are single amino acid residues or polypeptides they optionally are substituted at R^3 of substituents A^1, A^2 or A^3 in Formula I, or substituted at R_3 of substituents A_1, A_2 or A_3 in Formula II. These conjugates are generally produced by forming an amide bond between a carboxyl group of the amino acid (or C-terminal amino acid of a polypeptide for example). Alternatively, conjugates are formed between R^3

(Formula I) or R_3 (Formula II) and an amino group of an amino acid or polypeptide. Generally, only one of any site in the scaffold drug-like compound is amidated with an amino acid as described herein, although it is within the scope of this invention to introduce amino acids at more than one permitted site. Usually, a carboxyl group of R^3 is amidated with an amino acid. In general, the α-amino or α-carboxyl group of the amino acid or the terminal amino or carboxyl group of a polypeptide are bonded to the scaffold, parental functionalities. Carboxyl or amino groups in the amino acid side chains generally may be used to form the amide bonds with the parental compound or these groups may need to be protected during synthesis of the conjugates as described further below.

With respect to the carboxyl-containing side chains of amino acids or polypeptides it will be understood that the carboxyl group optionally will be blocked, e.g. by R^1, esterified with R^5 or amidated. Similarly, the amino side chains R^{16} optionally will be blocked with R^1 or substituted with R^5.

Such ester or amide bonds with side chain amino or carboxyl groups, like the esters or amides with the parental molecule, optionally are hydrolyzable *in vivo* or *in vitro* under acidic (pH <3) or basic (pH >10) conditions. Alternatively, they are substantially stable in the gastrointestinal tract of humans but are hydrolyzed enzymatically in blood or in intracellular environments. The esters or amino acid or polypeptide amidates also are useful as intermediates for the preparation of the parental molecule containing free amino or carboxyl groups. The free acid or base of the parental compound, for example, is readily formed from the esters or amino acid or polypeptide conjugates of this invention by conventional hydrolysis procedures.

When an amino acid residue contains one or more chiral centers, any of the D, L, meso, threo or erythro (as appropriate) racemates, scalemates or mixtures thereof may be used. In general, if the intermediates are to be hydrolyzed non-enzymatically (as would be the case where the amides are used as chemical intermediates for the free acids or free amines), D isomers are useful. On the other hand, L isomers are more versatile since they can be susceptible to both non-enzymatic and enzymatic hydrolysis, and are more efficiently transported by amino acid or dipeptidyl transport systems in the gastrointestinal tract.

Examples of suitable amino acids whose residues are represented by R^x or R^y include the following:

Glycine;

Aminopolycarboxylic acids, e.g., aspartic acid, β-hydroxyaspartic acid, glutamic acid, β -hydroxyglutamic acid, β-methylaspartic acid, β-methylglutamic acid, β, β-dimethylaspartic acid, γ-hydroxyglutamic acid, β, γ-dihydroxyglutamic acid, β -phenylglutamic acid, γ-methyleneglutamic acid, 3-aminoadipic acid, 2-aminopimelic acid, 2-aminosuberic acid and 2-aminosebacic acid;

Amino acid amides such as glutamine and asparagine;

Polyamino- or polybasic-monocarboxylic acids such as arginine, lysine, β -aminoalanine, γ -aminobutyrine, ornithine, citruline, homoarginine, homocitrulline, hydroxylysine, allohydroxylsine and diaminobutyric acid;

Other basic amino acid residues such as histidine;

Diaminodicarboxylic acids such as α, α'-diaminosuccinic acid, α, α'-diaminoglutaric acid, α, α'-diaminoadipic acid, α, α'-diaminopimelic acid, α, α'-diamino- β-hydroxypimelic acid, α, α'-diaminosuberic acid, α, α'-diaminoazelaic acid, and α, α'-diaminosebacic acid;

Imino acids such as proline, hydroxyproline, allohydroxyproline, γ-methylproline, pipecolic acid, 5-hydroxypipecolic acid, and azetidine-2-carboxylic acid;

A mono- or di-alkyl (typically C_1-C_8 branched or normal) amino acid such as alanine, valine, leucine, allylglycine, butyrine, norvaline, norleucine, heptyline, α-methylserine, α-amino-α-methyl-γ-hydroxyvaleric acid, α-amino- α-methyl-δ-hydroxyvaleric acid, α-amino-α-methyl-ε-hydroxycaproic acid, isovaline, α-methylglutamic acid, α-aminoisobutyric acid, α-aminodiethylacetic acid, α-aminodiisopropylacetic acid, α-aminodi-n-propylacetic acid, α-aminodiisobutylacetic acid, α-aminodi-n-butylacetic acid, α-aminoethylisopropylacetic acid, α-amino-n-propylacetic acid, α-aminodiisoamyacetic acid, α-methylaspartic acid, α-methylglutamic acid, 1-aminocyclopropane-1-carboxylic acid, isoleucine, alloisoleucine, *tert*-leucine, β-methyltryptophan and α-amino- β-ethyl-β-phenylpropionic acid;

β-phenylserinyl;

Aliphatic α-amino-β-hydroxy acids such as serine, β-hydroxyleucine, β-hydroxynorleucine, β -hydroxynorvaline, and α-amino-β-hydroxystearic acid;

α-Amino, α-, γ-, δ- or ε-hydroxy acids such as homoserine, δ -hydroxynorvaline, γ-hydroxynorvaline and ε-hydroxynorleucine residues; canavine and canaline; γ -hydroxyornithine;

2-hexosaminic acids such as D-glucosaminic acid or D-galactosaminic acid;

α-Amino-β-thiols such as penicillamine, β-thiolnorvaline or β-thiolbutyrine;

Other sulfur containing amino acid residues including cysteine; homocystine, β-phenylmethionine, methionine, S-allyl-L-cysteine sulfoxide, 2-thiolhistidine, cystathionine, and thiol ethers of cysteine or homocysteine;

Phenylalanine, tryptophan and ring-substituted α-amino acids such as the phenyl- or cyclohexylamino acids α-aminophenylacetic acid, α-aminocyclohexylacetic acid and α-amino-β-cyclohexylpropionic acid; phenylalanine analogues and derivatives comprising aryl, lower alkyl, hydroxy, guanidino, oxyalkylether, nitro, sulfur or halo-substituted phenyl (e.g., tyrosine, methyltyrosine and o-chloro-, p-chloro-, 3,4-dichloro, *o*-, *m*- or *p*-methyl-, 2,4,6-trimethyl-, 2-ethoxy-5-nitro-, 2-hydroxy-5-nitro- and p-nitro-phenylalanine); furyl-, thienyl-, pyridyl-, pyrimidinyl-, purinyl- or naphthyl-alanines; and tryptophan analogues and derivatives including kynurenine, 3-hydroxykynurenine, 2-hydroxytryptophan and 4-carboxytryptophan;

α-Amino substituted amino acids including sarcosine (N-methylglycine), N-benzylglycine, N-methylalanine, N-benzylalanine, N-methylphenylalanine, N-benzylphenylalanine, N-methylvaline and N-benzylvaline; and

α-Hydroxy and substituted α -hydroxy amino acids including serine, threonine, allothreonine, phosphoserine and phosphothreonine.

Polypeptides are polymers of amino acids in which a carboxyl group of one amino acid monomer is bonded to an amino or imino group of the next amino acid monomer by an amide bond. Polypeptides include dipeptides, low molecular weight polypeptides (about 1500-5000 MW) and proteins. Proteins optionally contain 3, 5, 10, 50, 75, 100 or more residues, and suitably are substantially sequence-homologous with human, animal, plant or microbial proteins. They include enzymes (e.g., hydrogen peroxidase) as well as immunogens such as KLH, or antibodies or proteins of any type against which one wishes to raise an immune response. The nature and identity of the polypeptide may vary widely.

The polypeptide amidates are useful as immunogens in raising antibodies against either the polypeptide (if it is not immunogenic in the animal to which it is administered) or against the epitopes on the remainder of the compound of this invention.

Antibodies capable of binding to the parental non-peptidyl compound are used to separate the parental compound from mixtures, for example in diagnosis or manufacturing of the parental compound. The conjugates of parental compound and polypeptide generally are more immunogenic than the polypeptides in closely homologous animals, and therefore make

the polypeptide more immunogenic for facilitating raising antibodies against it. Accordingly, the polypeptide or protein may be immunogenic in an animal typically used to raise antibodies, e.g., rabbit, mouse, horse, or rat. The polypeptide optionally contains a peptidolytic enzyme cleavage site at the peptide bond between the first and second residues adjacent to the acidic heteroatom. Such cleavage sites are flanked by enzymatic recognition structures, e.g. a particular sequence of residues recognized by a peptidolytic enzyme.

Peptidolytic enzymes for cleaving the polypeptide conjugates of this invention are well known, and in particular include carboxypeptidases, which digest polypeptides by removing C-terminal residues, and are specific in many instances for particular C-terminal sequences. Such enzymes and their substrate requirements in general are well known. For example, a dipeptide (having a given pair of residues and a free carboxyl terminus) is covalently bonded through its α-amino group to the phosphorus or carbon atoms of the compounds herein. In certain embodiments, a phosphonate group substituted with an amino acid or peptide will be cleaved by the appropriate peptidolytic enzyme, leaving the carboxyl of the proximal amino acid residue to autocatalytically cleave the phosphonoamidate bond.

Suitable dipeptidyl groups (designated by their single letter code) are AA, AR, AN, AD, AC, AE, AQ, AG, AH, AI, AL, AK, AM, AF, AP, AS, AT, AW, AY, AV, RA, RR, RN, RD, RC, RE, RQ, RG, RH, RI, RL, RK, RM, RF, RP, RS, RT, RW, RY, RV, NA, NR, NN, ND, NC, NE, NQ, NG, NH, NI, NL, NK, NM, NF, NP, NS, NT, NW, NY, NV, DA, DR, DN, DD, DC, DE, DQ, DG, DH, DI, DL, DK, DM, DF, DP, DS, DT, DW, DY, DV, CA, CR, CN, CD, CC, CE, CQ, CG, CH, CI, CL, CK, CM, CF, CP, CS, CT, CW, CY, CV, EA, ER, EN, ED, EC, EE, EQ, EG, EH, EI, EL, EK, EM, EF, EP, ES, ET, EW, EY, EV, QA, QR, QN, QD, QC, QE, QQ, QG, QH, QI, QL, QK, QM, QF, QP, QS, QT, QW, QY, QV, GA, GR, GN, GD, GC, GE, GQ, GG, GH, GI, GL, GK, GM, GF, GP, GS, GT, GW, GY, GV, HA, HR, HN, HD, HC, HE, HQ, HG, HH, HI, HL, HK, HM, HF, HP, HS, HT, HW, HY, HV, IA, IR, IN, ID, IC, IE, IQ, IG, IH, II, IL, IK, IM, IF, IP, IS, IT, IW, IY, IV, LA, LR, LN, LD, LC, LE, LQ, LG, LH, LI, LL, LK, LM, LF, LP, LS, LT, LW, LY, LV, KA, KR, KN, KD, KC, KE, KQ, KG, KH, KI, KL, KK, KM, KF, KP, KS, KT, KW, KY, KV, MA, MR, MN, MD, MC, ME, MQ, MG, MH, MI, ML, MK, MM, MF, MP, MS, MT, MW, MY, MV, FA, FR, FN, FD, FC, FE, FQ, FG, FH, FI, FL, FK, FM, FF, FP, FS, FT, FW, FY, FV, PA, PR, PN, PD, PC, PE, PQ, PG, PH, PI, PL, PK, PM, PF, PP, PS, PT, PW, PY, PV, SA, SR, SN, SD, SC, SE, SQ, SG, SH, SI, SL, SK, SM, SF, SP, SS, ST, SW, SY, SV, TA, TR, TN,

TD, TC, TE, TQ, TG, TH, TI, TL, TK, TM, TF, TP, TS, TT, TW, TY, TV, WA, WR, WN, WD, WC, WE, WQ, WG, WH, WI, WL, WK, WM, WF, WP, WS, WT, WW, WY, WV, YA, YR, YN, YD, YC, YE, YQ, YG, YH, YI, YL, YK, YM, YF, YP, YS, YT, YW, YY, YV, VA, VR, VN, VD, VC, VE, VQ, VG, VH, VI, VL, VK, VM, VF, VP, VS, VT, VW, VY and VV.

Tripeptide residues are also useful as protecting groups. When a phosphonate is to be protected, the sequence -X^4-pro-X^5- (where X^4 is any amino acid residue and X^5 is an amino acid residue, a carboxyl ester of proline, or hydrogen) will be cleaved by luminal carboxypeptidase to yield X^4 with a free carboxyl, which in turn is expected to autocatalytically cleave the phosphonoamidate bond. The carboxy group of X^5 optionally is esterified with benzyl.

Dipeptide or tripeptide species can be selected on the basis of known transport properties and/or susceptibility to peptidases that can affect transport to intestinal mucosal or other cell types. Dipeptides and tripeptides lacking an α-amino group are transport substrates for the peptide transporter found in brush border membrane of intestinal mucosal cells (Bai, J.P.F., (1992) *Pharm Res.* 9:969-978. Transport competent peptides can thus be used to enhance bioavailability of the amidate compounds. Di- or tripeptides having one or more amino acids in the D configuration may be compatible with peptide transport. Amino acids in the D configuration can be used to reduce the susceptibility of a di- or tripeptide to hydrolysis by proteases common to the brush border such as aminopeptidase N. In addition, di- or tripeptides alternatively are selected on the basis of their relative resistance to hydrolysis by proteases found in the lumen of the intestine. For example, tripeptides or polypeptides lacking asp and/or glu are poor substrates for aminopeptidase A, di- or tripeptides lacking amino acid residues on the N-terminal side of hydrophobic amino acids (leu, tyr, phe, val, trp) are poor substrates for endopeptidase, and peptides lacking a pro residue at the penultimate position at a free carboxyl terminus are poor substrates for carboxypeptidase P. Similar considerations can also be applied to the selection of peptides that are either relatively resistant or relatively susceptible to hydrolysis by cytosolic, renal, hepatic, serum or other peptidases. Such poorly cleaved polypeptide amidates are immunogens or are useful for bonding to proteins in order to prepare immunogens.

<u>Phosphonate analogs of known experimental or approved Protease Inhibitor Drugs</u>

The known experimental or approved protease inhibitor drugs which can be derivatized in accord with the present invention must contain at least one functional group capable of linking, i.e. bonding to the phosphorus atom in the phosphonate moiety. The phosphonate derivatives of Formulas I-VIII may cleave *in vivo* in stages after they have reached the desired site of action, i.e. inside a cell. One mechanism of action inside a cell may entail a first cleavage, e.g. by esterase, to provide a negatively-charged "locked-in" intermediate. Cleavage of a terminal ester grouping in Formulas I-VIII thus affords an unstable intermediate which releases a negatively charged "locked in" intermediate.

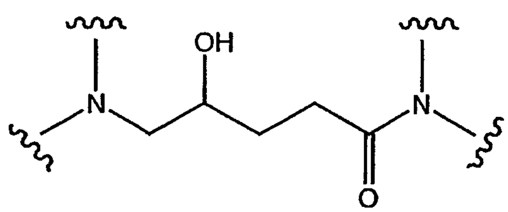
After passage inside a cell, intracellular enzymatic cleavage or modification of the phosphonate prodrug compound may result in an intracellular accumulation of the cleaved or modified compound by a "trapping" mechanism. The cleaved or modified compound may then be "locked-in" the cell, i.e. accumulate in the cell by a significant change in charge, polarity, or other physical property change which decreases the rate at which the cleaved or modified compound can exit the cell, relative to the rate at which it entered as the phosphonate prodrug. Other mechanisms by which a therapeutic effect is achieved may be operative as well. Enzymes which are capable of an enzymatic activation mechanism with the phosphonate prodrug compounds of the invention include, but are not limited to, amidases, esterases, microbial enzymes, phospholipases, cholinesterases, and phosphatases.

In selected instances in which the drug is of the nucleoside type, such as is the case of zidovudine and numerous other antiretroviral agents, it is known that the drug is activated *in vivo* by phosphorylation. Such activation may occur in the present system by enzymatic conversion of the "locked-in" intermediate with phosphokinase to the active phosphonate diphosphate and/or by phosphorylation of the drug itself after its release from the "locked-in" intermediate as described above. In either case, the original nucleoside-type drug will be converted, via the derivatives of this invention, to the active phosphorylated species.

From the foregoing, it will be apparent that many structurally different known approved and experimental HIV protease inhibitor drugs can be derivatized in accord with the present invention. Numerous such drugs are specifically mentioned herein. However, it should be understood that the discussion of drug families and their specific members for derivatization according to this invention is not intended to be exhaustive, but merely illustrative.

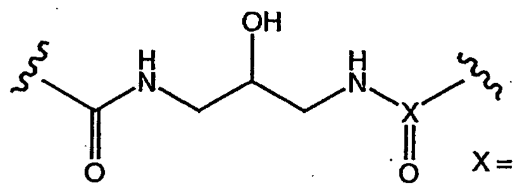
As another example, when the selected drug contains multiple reactive hydroxyl functions, a mixture of intermediates and final products may again be obtained. In the unusual case in which all hydroxy groups are approximately equally reactive, there is not expected to be a single, predominant product, as each mono-substituted product will be obtained in approximate by equal amounts, while a lesser amount of multiply-substituted product will also result. Generally speaking, however, one of the hydroxyl groups will be more susceptible to substitution than the other(s), e.g. a primary hydroxyl will be more reactive than a secondary hydroxyl, an unhindered hydroxyl will be more reactive than a hindered one. Consequently, the major product will be a mono-substituted one in which the most reactive hydroxyl has been derivatized while other mono-substituted and multiply-substituted products may be obtained as minor products.

Formula I compounds having a 3-hydroxy-5-amino-pentamide core include Indinavir-like phosphonate protease inhibitors (ILPPI). Compounds of the invention include phosphonate analogs of other known PI compounds with a 3-hydroxy-5-amino-pentamide core which have been identified as CGP-49689, CGP-53437, CGP-57813 (Novartis); L-689502, L-693549, L-748496, L-754394, MK-944a, Iddb63, Iddb88 (Merck); Lasinavir (Bristol-Myers Squibb); U-81749 (PNU/Pfizer); SB-203386, SKF-108922 (SmithKline Beecham).



I

Formula II compounds having a 2-hydroxy-1, 3-amino-propylamide or 2-hydroxy-1,3-amino-propylaminosulfone core include Amprenavir-like phosphonate protease inhibitors (AMLPPI). Compounds of the invention include phosphonate analogs of other known PI compounds with a 2-hydroxy-3-amido-propylamide or 2-hydroxy-3-amido-propylaminosulfone core which have been identified as Droxinavir, Telinavir, Iddb51 (Searle); Ph4556 (WO 95/29922; Ph5145 (WO 96/31527; DPC-681, DPC-684 (DuPont); VB-11328 (Vertex); TMC-114 (Tibotech/Johnson & Johnson). Formula II compounds also include phosphonate analogs of fosamprenavir where the 2-hydroxy is phosphorylated, i.e. having a or 2-phosphate-1,3-amino-propylaminosulfone core (US Patent No. 6,436,989).



X = C, SO II

The embodiments of the invention also include the following phosphonate analogs of Formula II, represented as Formulas IIa-Ig:

$$A{-}(B)_x{-}\underset{\displaystyle H}{\underset{|}{N}}{-}\overset{\displaystyle D}{\overset{|}{CH}}{-}\underset{\displaystyle OH}{\underset{|}{CH}}{-}CH_2{-}\underset{\displaystyle D'}{\underset{|}{N}}{-}SO_2{-}E \qquad \text{IIa}$$

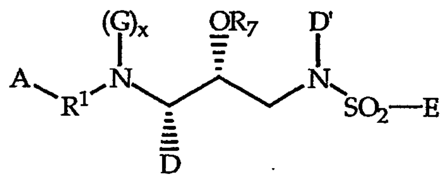
described as "(I)" in: WO 94/05639 (published 17 March 1994) at page 4, line 15, to page 6, line 27, page 15, line 21, to page 17, line 33, and Claim 1; US Patent No. 5,585,397 (issued 17 December 1996) at col. 2, line 45, to col. 3, line 53, and col. 8, line 1, to col. 9, line 12; US Patent No. 5,783, 701 (issued 21 July 1998) at col. 2, line 43, to col. 3, line 64, col. 8, line 13, to col. 9, line 33, and Claim 1; US Patent No. 5,856,353 (issued 5 January 1999) at col. 2, line 45, to col. 3, line 65, col. 8, line 14, to col. 9, line 37, and Claim 1; US Patent No. 5,977,137 (issued 2 November 1999) at col. 2, line 43, to col. 3, line 65, col. 8, line 15, to col. 9, line 38, and Claim 1; and US Patent No. 6,004,957 (issued 21 December 1999) at col. 2, line 47, to col. 4, line 3, col. 8, line 18, to col. 9, line 41, and Claim 1 therein.

$$THF{-}R^1{-}NH{-}\overset{\displaystyle D}{\overset{|}{CH}}{-}\overset{\displaystyle OH}{\overset{|}{CH}}{-}CH_2{-}\overset{\displaystyle D'}{\overset{|}{N}}{-}SO_2{-}E \qquad \text{IIb}$$

described as "(I)" in: WO 96/33184 (published 24 October 1996) at page 4, line 19, to page 6, line 5, page 17, line 11, to page 19, line 31, and Claim 1; and US Patent No. 5,723,490 (issued 3 March 1998) at col. 2, line 49, to col. 3, line 39, col. 8, line 66, to col. 10, line 36, and Claim 1.

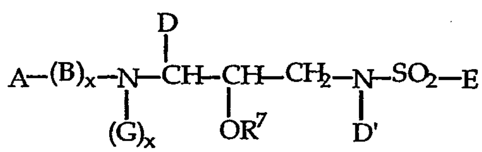
$$A{-}R^1{-}NH{-}\overset{\displaystyle D}{\overset{|}{CH}}{-}\overset{\displaystyle OH}{\overset{|}{CH}}{-}CH_2{-}\overset{\displaystyle D'}{\overset{|}{N}}{-}SO_2{-}E \qquad \text{IIc}$$

described as "(I)" in: WO 96/33187 (published 24 October 1996) at page 4, line 23, to page 6, line 18, page 18, line 8, to page 21, line 18, and Claims 1 and 6; US Patent No. 5,691,372 (issued 25 November 1997) at col. 2, line 43, to col. 3, line 47, col. 9, line 21, to col. 11, line 5, and Claims 1 and 5; and US Patent No. 5,990,155 (issued 23 November 1999) at col. 2, line 46, to col. 3, line 55, col. 9, line 25, to col. 11, line 13, and Claims 1 and 3.



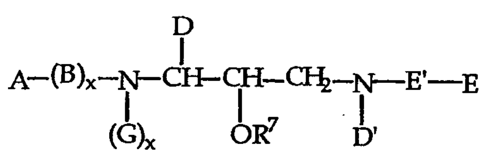
IId

described as "(I)" in: WO 99/33793 (published 8 July 1999) at page 4, line 1, to page 7, line 29, page 17, line 1, to page 20, line 33, and Claim 1.



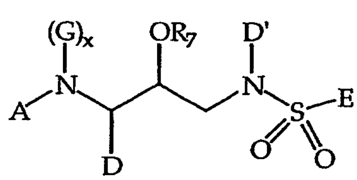
IIe

described as "(I)" in: WO 99/33815 (published 8 July 1999) at page 4, line 1, to page 7, line 19, page 12, line 18, to page 16, line 7, and Claim 1; and WO 99/65870 (published 23 December 1999) at page 4, line 7, to page 8, line 4, page 12, line 7, to page 16, line 4, and Claim 1.



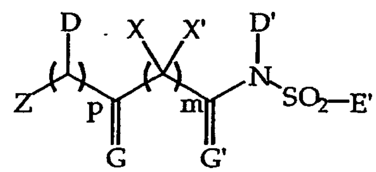
IIf

described as "(I)" in: WO 00/47551 (published 17 August 2000) at page 4, line 10, to page 8, line 29, page 13, line 14, to page 17, line 32, and Claim 1.



IIg

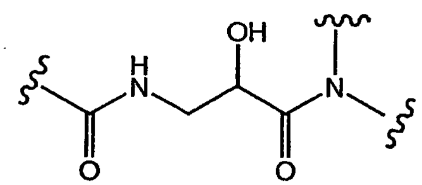
described as "(I)" in: WO 00/76961 (published 21 December 2000) at page 5, line 1, to page 10, line 24, page 14, line 28, to page 20, line 21, and Claim 1.



IIh

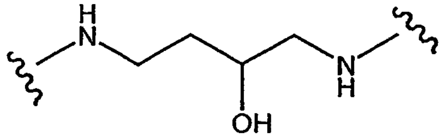
described as "(I)" in: WO 99/33792 (published 8 July 1999) at page 4, line 5, to page 7, line 35, page 17, line 10, to page 21, line 6, and Claim 1; WO 95/24385 (published 14 September 1995) at page 4, line 24, to page 7, line 14, page 16, line 20, to page 19, line 8, and Claims 1 and 29; and US Patent No. 6,127,372 (issued 3 October 2000) at col. 2, line 58, to col. 4, line 28, col. 8, line 66, to col. 10, line 37, and Claim 1.

Formula III compounds having a 2-hydroxy-3-amino-propylamide core include KNI-like phosphonate protease inhibitors (KNILPPI). Compounds of the invention include phosphonate analogs of other known PI compounds with a 2-hydroxy-3-amido-propylamide or 2-hydroxy-3-amido-propylaminosulfone core which have been identified as KNI-764 (JE-2147, AG1776); KNI-102, KNI-227, KNI-241, KNI-272, KNI-413, KNI-549, KNI-577, KNI-727, JE-2178 (Japan Energy); Ph3939 (EP 587311); R-87366, Iddb134 (Sankyo); VLE-776 (Scripps Institute).



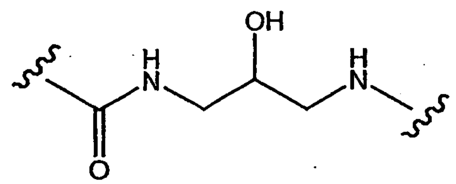
III

Formula IV compounds having a 2-hydroxy-4-amino-butylamine core include Ritonavir-like phosphonate protease inhibitors (RLPPI) and Lopinavir-like phosphonate protease inhibitors (LLPPI). Compounds of the invention include phosphonate analogs of other known PI compounds with a 2-hydroxy-4-amino-butylamine core which have been identified as A-76928, A-80735, A-80987 (Abbott Laboratories).



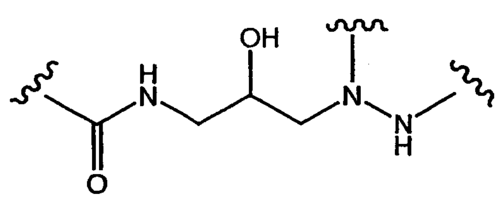
IV

Formula V compounds having an acylated 1,3-diaminopropane core include Saquinavir-like phosphonate protease inhibitors (SLPPI) and Nelfinavir-like phosphonate protease inhibitors (NLPPI). Compounds of the invention include phosphonate analogs of other known PI compounds with an acylated 1,3-diaminopropane core which have been identified as Ro-33-2910, Ro-33-4649 (Hofman La Roche); BMS-182193, BMS-186318, BMS-187071 (Bristol-Myers Squibb); JG-365 (Univ. of Wisconsin); L-704325, L-738872, L-739594, L-743770 (Merck & Co.); LB-71206 (LG Chemical Ltd.); LY-296242, LY-314163, LY-316683, LY-326620 (Eli Lilly Co.), Palinavir (BioMega/BI); Ph5640, Ph6090 (WO 97/21100).



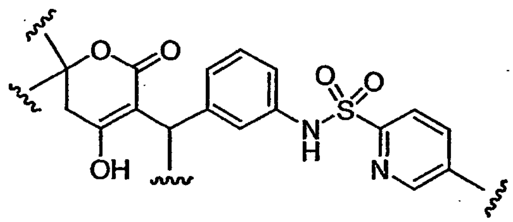
V

Formula VI compounds having a 2-hydroxy-3-diaza-propylamide core include Atazanavir-like phosphonate protease inhibitors (ATLPPI). Compounds of the invention include phosphonate analogs of other known PI compounds with a 2-hydroxy-3-diaza-propylamide core which have been identified as CGP-56603, CGP-53820, CGP-70726 (Novartis), ABT-538 (Abbott Laboratories), and DG-35 (National Cancer Institute).



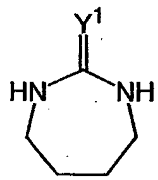
VI

Formula VII compounds having sulfonamide 5,6-dihydro-4-hydroxy-2-pyrone core include Tipranavir-like phosphonate protease inhibitors (TLPPI).

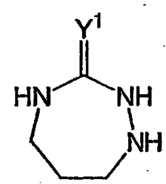


VII

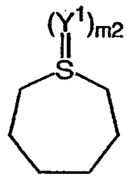
Formula VIII compounds have a six or seven-membered ring, cyclic carbonyl, sulfone, or sulfonyl core, where Y^1 is oxygen, sulfur, or substituted nitrogen and M2 is 1 or 2. The invention includes Cyclic carbonyl-like phosphonate protease inhibitor compounds (CCLPPI), e.g. Formula VIIIa-d.



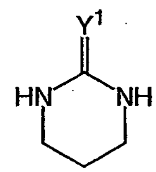
VIIIa



VIIIb

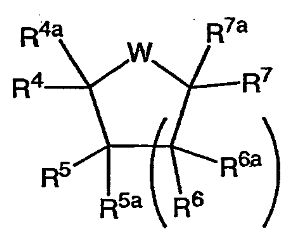


VIIIc and



VIIId;

Cyclic carbonyl protease inhibitors without a phosphonate group are described in US Patent Nos. RE37781; 6,503,898; 5,880,295; 5,811,422; 5,610,294; 5,559,252; and 5,506,355, as well as patent applications and granted patents which are equivalents of, or related by priority claims thereto. CCLPPI compounds also include phosphonate analogs of:



described as "(I)" in WO 94/19329 (published 1 September 1994) at page 4, line 23, to page 21, line 16 and Claim 1. Also contemplated are patent applications and granted patents which are equivalents of or related by priority claims to WO 94/19329.

Stereoisomers

The compounds of the invention, exemplified by Formula I and II, may have chiral centers, e.g. chiral carbon or phosphorus atoms. The compounds of the invention thus include racemic mixtures of all stereoisomers, including enantiomers, diastereomers, and atropisomers. In addition, the compounds of the invention include enriched or resolved optical isomers at any or all asymmetric, chiral atoms. In other words, the chiral centers apparent from the depictions are provided as the chiral isomers or racemic mixtures. Both racemic and diastereomeric mixtures, as well as the individual optical isomers isolated or synthesized, substantially free of their enantiomeric or diastereomeric partners, are all within the scope of the invention. The racemic mixtures are separated into their individual, substantially optically pure isomers through well-known techniques such as, for example, the separation of diastereomeric salts formed with optically active adjuncts, e.g., acids or bases followed by conversion back to the optically active substances. In most instances, the desired optical isomer is synthesized by means of stereospecific reactions, beginning with the appropriate stereoisomer of the desired starting material.

The compounds of the invention can also exist as tautomeric isomers in certain cases. All though only one delocalized resonance structure may be depicted, all such forms are contemplated within the scope of the iinvention. For example, ene-amine tautomers can exist for purine, pyrimidine, imidazole, guanidine, amidine, and tetrazole systems and all their possible tautomeric forms are within the scope of the invention.

Salts and Hydrates

The compositions of this invention optionally comprise salts of the compounds herein, especially pharmaceutically acceptable non-toxic salts containing, for example, Na^+, Li^+, K^+, Ca^{+2} and Mg^{+2}. Such salts may include those derived by combination of appropriate cations such as alkali and alkaline earth metal ions or ammonium and quaternary amino ions with an acid anion moiety, typically a carboxylic acid. Monovalent salts are preferred if a water soluble salt is desired.

Metal salts typically are prepared by reacting the metal hydroxide with a compound of this invention. Examples of metal salts which are prepared in this way are salts containing Li^+, Na^+, and K^+. A less soluble metal salt may be precipitated from the solution of a more soluble salt by addition of the suitable metal compound.

In addition, salts may be formed from acid addition of certain organic and inorganic

acids, e.g., HCl, HBr, H_2SO_4, H_3PO_4 or organic sulfonic acids, to basic centers, typically amines, or to acidic groups. Finally, it is to be understood that the compositions herein comprise compounds of the invention in their un-ionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

Also included within the scope of this invention are the salts of the parental compounds with one or more amino acids. Any of the amino acids described above are suitable, especially the naturally-occurring amino acids found as protein components, although the amino acid typically is one bearing a side chain with a basic or acidic group, e.g., lysine, arginine or glutamic acid, or a neutral group such as glycine, serine, threonine, alanine, isoleucine, or leucine.

Methods of Inhibition of HIV Protease

Another aspect of the invention relates to methods of inhibiting the activity of HIV protease comprising the step of treating a sample suspected of containing HIV with a composition of the invention.

Compositions of the invention may act as inhibitors of HIV protease, as intermediates for such inhibitors or have other utilities as described below. The inhibitors will bind to locations on the surface or in a cavity of HIV protease having a geometry unique to HIV protease. Compositions binding HIV protease may bind with varying degrees of reversibility. Those compounds binding substantially irreversibly are ideal candidates for use in this method of the invention. Once labeled, the substantially irreversibly binding compositions are useful as probes for the detection of HIV protease. Accordingly, the invention relates to methods of detecting HIV protease in a sample suspected of containing HIV protease comprising the steps of: treating a sample suspected of containing HIV protease with a composition comprising a compound of the invention bound to a label; and observing the effect of the sample on the activity of the label. Suitable labels are well known in the diagnostics field and include stable free radicals, fluorophores, radioisotopes, enzymes, chemiluminescent groups and chromogens. The compounds herein are labeled in conventional fashion using functional groups such as hydroxyl, carboxyl, sulfhydryl or amino.

Within the context of the invention, samples suspected of containing HIV protease include natural or man-made materials such as living organisms; tissue or cell cultures; biological samples such as biological material samples (blood, serum, urine, cerebrospinal

fluid, tears, sputum, saliva, tissue samples, and the like); laboratory samples; food, water, or air samples; bioproduct samples such as extracts of cells, particularly recombinant cells synthesizing a desired glycoprotein; and the like. Typically the sample will be suspected of containing an organism which produces HIV protease, frequently a pathogenic organism such as HIV. Samples can be contained in any medium including water and organic solvent\water mixtures. Samples include living organisms such as humans, and man made materials such as cell cultures.

The treating step of the invention comprises adding the composition of the invention to the sample or it comprises adding a precursor of the composition to the sample. The addition step comprises any method of administration as described above.

If desired, the activity of HIV protease after application of the composition can be observed by any method including direct and indirect methods of detecting HIV protease activity. Quantitative, qualitative, and semiquantitative methods of determining HIV protease activity are all contemplated. Typically one of the screening methods described above are applied, however, any other method such as observation of the physiological properties of a living organism are also applicable.

Organisms that contain HIV protease include the HIV virus. The compounds of this invention are useful in the treatment or prophylaxis of HIV infections in animals or in man.

However, in screening compounds capable of inhibiting human immunodeficiency viruses, it should be kept in mind that the results of enzyme assays may not correlate with cell culture assays. Thus, a cell based assay should be the primary screening tool.

Screens for HIV protease Inhibitors.

Compositions of the invention are screened for inhibitory activity against HIV protease by any of the conventional techniques for evaluating enzyme activity. Within the context of the invention, typically compositions are first screened for inhibition of HIV protease *in vitro* and compositions showing inhibitory activity are then screened for activity *in vivo*. Compositions having *in vitro* Ki (inhibitory constants) of less then about 5×10^{-6} M, typically less than about 1×10^{-7} M and preferably less than about 5×10^{-8} M are preferred for *in vivo* use.

Useful *in vitro* screens have been described in detail and will not be elaborated here. However, the examples describe suitable *in vitro* assays.

Pharmaceutical Formulations

The compounds of this invention are formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations will optionally contain excipients such as those set forth in the "Handbook of Pharmaceutical Excipients" (1986). Excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextran, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10.

While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, of the invention comprise at least one active ingredient, as above defined, together with one or more acceptable carriers therefor and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, PA). Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

A tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom.

For infections of the eye or other external tissues e.g. mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, i.e. an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulphoxide and related analogs.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Emulgents and emulsion stabilizers suitable for use in the formulation of the invention include Tween® 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. The cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils are used.

Pharmaceutical formulations according to the present invention comprise a combination according to the invention together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a

longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions of the invention contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcelluose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl p-hydroxy-benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules of the invention suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a

mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

The pharmaceutical compositions of the invention may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 μg of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such

formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10%, and particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns, such as 0.5, 1, 30, 35 etc., which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis of HIV infections as described below.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

The formulations are presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

The invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefor.

Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

Compounds of the invention are used to provide controlled release pharmaceutical formulations containing as active ingredient one or more compounds of the invention ("controlled release formulations") in which the release of the active ingredient are controlled and regulated to allow less frequency dosing or to improve the pharmacokinetic or toxicity profile of a given active ingredient.

Effective dose of active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses) or against an active viral infection, the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies. It can be expected to be from about 0.0001 to about 100 mg/kg body weight per day. Typically, from about 0.01 to about 10 mg/kg body weight per day. More typically, from about .01 to about 5 mg/kg body weight per day. More typically, from about .05 to about 0.5 mg/kg body weight per day. For example, the daily candidate dose for an adult human of approximately 70 kg body weight will range from 1 mg to 1000 mg, preferably between 5 mg and 500 mg, and may take the form of single or multiple doses.

Routes of Administration

One or more compounds of the invention (herein referred to as the active ingredients) are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the

condition of the recipient. An advantage of the compounds of this invention is that they are orally bioavailable and can be dosed orally.

Combination Therapy

Compositions of the invention are also used in combination with other active ingredients. Such combinations are selected based on the condition to be treated, cross-reactivities of ingredients and pharmaco-properties of the combination. For example, when treating viral infections the compositions of the invention may be combined with other antivirals such as other protease inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors or HIV integrase inhibitors.

It is possible to combine any compound of the invention with one or more other active ingredients in a unitary dosage form for simultaneous or sequential administration to an HIV infected patient. The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations. Second and third active ingredients in the combination may have anti-HIV activity. Exemplary active ingredients to be administered in combination with compounds of the invention are protease inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and HIV integrase inhibitors.

The combination therapy may provide "synergy" and "synergistic", i.e. the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect may be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be attained when the compounds are administered or delivered sequentially, e.g. in separate tablets, pills or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, i.e. serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together. A synergistic anti-viral effect denotes an antiviral effect which is greater than the predicted purely additive effects of the individual compounds of the combination.

Metabolites of the Compounds of the Invention

Also falling within the scope of this invention are the *in vivo* metabolic products of the compounds described herein, to the extent such products are novel and unobvious over the prior art. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes novel and unobvious compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled (e.g. ^{14}C or ^{3}H) compound of the invention, administering it parenterally in a detectable dose (e.g. greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, e.g. by MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found *in vivo*, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention even if they possess no HIV protease inhibitory activity of their own.

Recipes and methods for determining stability of compounds in surrogate gastrointestinal secretions are known. Compounds are defined herein as stable in the gastrointestinal tract where less than about 50 mole percent of the protected groups are deprotected in surrogate intestinal or gastric juice upon incubation for 1 hour at 37°C. Simply because the compounds are stable to the gastrointestinal tract does not mean that they cannot be hydrolyzed *in vivo*. The phosphonate prodrugs of the invention typically will be stable in the digestive system but may be substantially hydrolyzed to the parental drug in the digestive lumen, liver or other metabolic organ, or within cells in general.

Exemplary Methods of Making the Compounds of the Invention.

The invention provides many methods of making the compositions of the invention. The compositions are prepared by any of the applicable techniques of organic synthesis. Many such techniques are well known in the art, such as those elaborated in "Compendium of Organic Synthetic Methods" (John Wiley & Sons, New York), Vol. 1, Ian T. Harrison and

Shuyen Harrison, 1971; Vol. 2, Ian T. Harrison and Shuyen Harrison, 1974; Vol. 3, Louis S. Hegedus and Leroy Wade, 1977; Vol. 4, Leroy G. Wade, jr., 1980; Vol. 5, Leroy G. Wade, Jr., 1984; and Vol. 6, Michael B. Smith; as well as March, J., "Advanced Organic Chemistry, Third Edition", (John Wiley & Sons, New York, 1985), "Comprehensive Organic Synthesis. Selectivity, Strategy & Efficiency in Modern Organic Chemistry. In 9 Volumes", Barry M. Trost, Editor-in-Chief (Pergamon Press, New York, 1993 printing).

Dialkyl phosphonates may be prepared according to the methods of: Quast et al (1974) *Synthesis* 490; Stowell et al (1990) *Tetrahedron Lett.* 3261; US Patent No. 5,663,159.

In general, synthesis of phosphonate esters is achieved by coupling a nucleophile amine or alcohol with the corresponding activated phosphonate electrophilic precursor. For example, chlorophosphonate addition on to 5'-hydroxy of nucleoside is a well known method for preparation of nucleoside phosphate monoesters. The activated precursor can be prepared by several well known methods. Chlorophosphonates useful for synthesis of the prodrugs are prepared from the substituted-1,3-propanediol (Wissner, et al, (1992) *J. Med Chem.* 35:1650). Chlorophosphonates are made by oxidation of the corresponding chlorophospholanes (Anderson, et al, (1984) *J. Org. Chem.* 49:1304) which are obtained by reaction of the substituted diol with phosphorus trichloride. Alternatively, the chlorophosphonate agent is made by treating substituted-1,3-diols with phosphorusoxychloride (Patois, et al, (1990) *J. Chem. Soc. Perkin Trans. I*, 1577). Chlorophosphonate species may also be generated in situ from corresponding cyclic phosphites (Silverburg, et al., (1996) *Tetrahedron Lett.*, 37:771-774), which in turn can be either made from chlorophospholane or phosphoramidate intermediate. Phosphoroflouridate intermediate prepared either from pyrophosphate or phosphoric acid may also act as precursor in preparation of cyclic prodrugs (Watanabe et al., (1988) *Tetrahedron Lett.*, 29:5763-66). <u>Caution</u>: fluorophosphonate compounds may be highly toxic!

Phosphonate prodrugs of the present invention may also be prepared from the precursor free acid by Mitsunobu reactions (Mitsunobu, (1981) *Synthesis*, 1; Campbell, (1992) *J. Org. Chem.*, 52:6331), and other acid coupling reagents including, but not limited to, carbodiimides (Alexander, et al, (1994) *Collect. Czech. Chem. Commun.* 59:1853; Casara, et al, (1992) *Bioorg. Med. Chem. Lett.*, 2:145; Ohashi, et al, (1988) *Tetrahedron Lett.*, 29:1189), and benzotriazolyloxytris-(dimethylamino)phosphonium salts (Campagne, et al, (1993) *Tetrahedron Lett.*, 34:6743).

Aryl halides undergo Ni^{+2} catalyzed reaction with phosphite derivatives to give aryl phosphonate containing compounds (Balthazar, et al (1980) *J. Org. Chem.* 45:5425). Phosphonates may also be prepared from the chlorophosphonate in the presence of a palladium catalyst using aromatic triflates (Petrakis, et al, (1987) *J. Am. Chem. Soc.* 109:2831; Lu, et al, (1987) *Synthesis*, 726). In another method, aryl phosphonate esters are prepared from aryl phosphates under anionic rearrangement conditions (Melvin (1981) *Tetrahedron Lett.* 22:3375; Casteel, et al, (1991) *Synthesis*, 691). N-Alkoxy aryl salts with alkali metal derivatives of cyclic alkyl phosphonate provide general synthesis for heteroaryl-2-phosphonate linkers (Redmore (1970) *J. Org. Chem.* 35:4114). These above mentioned methods can also be extended to compounds where the W^5 group is a heterocycle. Cyclic-1,3-propanyl prodrugs of phosphonates are also synthesized from phosphonic diacids and substituted propane-1,3-diols using a coupling reagent such as 1,3-dicyclohexylcarbodiimide (DCC) in presence of a base (e.g., pyridine). Other carbodiimide based coupling agents like 1,3-disopropylcarbodiimide or water soluble reagent, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) can also be utilized for the synthesis of cyclic phosphonate prodrugs.

The carbamoyl group may be formed by reaction of a hydroxy group according to the methods known in the art, including the teachings of Ellis, US 2002/0103378 A1 and Hajima, US Patent No. 6,018,049.

Schemes and Examples

A number of exemplary methods for the preparation of the compositions of the invention are provided below. These methods are intended to illustrate the nature of such preparations are not intended to limit the scope of applicable methods.

General aspects of these exemplary methods are described below and in the Examples. Each of the products of the following processes is optionally separated, isolated, and/or purified prior to its use in subsequent processes.

Generally, the reaction conditions such as temperature, reaction time, solvents, work-up procedures, and the like, will be those common in the art for the particular reaction to be performed. The cited reference material, together with material cited therein, contains detailed descriptions of such conditions. Typically the temperatures will be -100°C to 200°C, solvents will be aprotic or protic, and reaction times will be 10 seconds to 10 days. Work-up typically consists of quenching any unreacted reagents followed by partition between a

water/organic layer system (extraction) and separating the layer containing the product.

Oxidation and reduction reactions are typically carried out at temperatures near room temperature (about 20°C), although for metal hydride reductions frequently the temperature is reduced to 0°C to -100°C, solvents are typically aprotic for reductions and may be either protic or aprotic for oxidations. Reaction times are adjusted to achieve desired conversions.

Condensation reactions are typically carried out at temperatures near room temperature, although for non-equilibrating, kinetically controlled condensations reduced temperatures (0°C to -100°C) are also common. Solvents can be either protic (common in equilibrating reactions) or aprotic (common in kinetically controlled reactions).

Standard synthetic techniques such as azeotropic removal of reaction by-products and use of anhydrous reaction conditions (e.g. inert gas environments) are common in the art and will be applied when applicable.

The terms "treated", "treating", "treatment", and the like, mean contacting, mixing, reacting, allowing to react, bringing into contact, and other terms common in the art for indicating that one or more chemical entities is treated in such a manner as to convert it to one or more other chemical entities. This means that "treating compound one with compound two" is synonymous with "allowing compound one to react with compound two", "contacting compound one with compound two", "reacting compound one with compound two", and other expressions common in the art of organic synthesis for reasonably indicating that compound one was "treated", "reacted", "allowed to react", etc., with compound two.

"Treating" indicates the reasonable and usual manner in which organic chemicals are allowed to react. Normal concentrations (0.01M to 10M, typically 0.1M to 1M), temperatures (-100°C to 250°C, typically -78°C to 150°C, more typically -78°C to 100°C, still more typically 0°C to 100°C), reaction vessels (typically glass, plastic, metal), solvents, pressures, atmospheres (typically air for oxygen and water insensitive reactions or nitrogen or argon for oxygen or water sensitive), etc., are intended unless otherwise indicated. The knowledge of similar reactions known in the art of organic synthesis are used in selecting the conditions and apparatus for "treating" in a given process. In particular, one of ordinary skill in the art of organic synthesis selects conditions and apparatus reasonably expected to successfully carry out the chemical reactions of the described processes based on the knowledge in the art.

Modifications of each of the exemplary schemes above and in the examples (hereafter

"exemplary schemes") leads to various analogs of the specific exemplary materials produce. The above cited citations describing suitable methods of organic synthesis are applicable to such modifications.

In each of the exemplary schemes it may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example: reverse-phase and normal phase; size exclusion; ion exchange; high, medium, and low pressure liquid chromatography methods and apparatus; small scale analytical; simulated moving bed (SMB) and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography.

Another class of separation methods involves treatment of a mixture with a reagent selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product, or the like. Such reagents include adsorbents or absorbents such as activated carbon, molecular sieves, ion exchange media, or the like. Alternatively, the reagents can be acids in the case of a basic material, bases in the case of an acidic material, binding reagents such as antibodies, binding proteins, selective chelators such as crown ethers, liquid/liquid ion extraction reagents (LIX), or the like.

Selection of appropriate methods of separation depends on the nature of the materials involved. For example, boiling point, and molecular weight in distillation and sublimation, presence or absence of polar functional groups in chromatography, stability of materials in acidic and basic media in multiphase extraction, and the like. One skilled in the art will apply techniques most likely to achieve the desired separation.

A single stereoisomer, e.g. an enantiomer, substantially free of its stereoisomer may be obtained by resolution of the racemic mixture using a method such as formation of diastereomers using optically active resolving agents ("Stereochemistry of Carbon Compounds," (1962) by E. L. Eliel, McGraw Hill; Lochmuller, C. H., (1975) *J. Chromatogr.*, 113:(3) 283-302). Racemic mixtures of chiral compounds of the invention can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2)

formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions.

Under method (1), diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, α-methyl-β-phenylethylamine (amphetamine), and the like with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts.

Alternatively, by method (2), the substrate to be resolved is reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S. (1994) Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the free, enantiomerically enriched xanthene. A method of determining optical purity involves making chiral esters, such as a menthyl ester, e.g. (-) menthyl chloroformate in the presence of base, or Mosher ester, α-methoxy-α-(trifluoromethyl)phenyl acetate (Jacob III. (1982) *J. Org. Chem.* 47:4165), of the racemic mixture, and analyzing the NMR spectrum for the presence of the two atropisomeric diastereomers. Stable diastereomers of atropisomeric compounds can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (Hoye, T., WO 96/15111). By method (3), a racemic mixture of two enantiomers can be separated by chromatography using a chiral stationary phase (Chiral Liquid Chromatography (1989) W. J. Lough, Ed. Chapman and Hall, New York; Okamoto, (1990) *J. of Chromatogr.* 513:375-378). Enriched or purified enantiomers can be distinguished by methods used to distinguish other chiral molecules with asymmetric carbon atoms, such as optical rotation and circular dichroism.

All literature and patent citations above are hereby expressly incorporated by reference at the locations of their citation. Specifically cited sections or pages of the above cited works are incorporated by reference with specificity. The invention has been described

in detail sufficient to allow one of ordinary skill in the art to make and use the subject matter of the following Embodiments. It is apparent that certain modifications of the methods and compositions of the following Embodiments can be made within the scope and spirit of the invention.

Examples General Section

The following Examples refer to the Schemes.

Some Examples have been performed multiple times. In repeated Examples, reaction conditions such as time, temperature, concentration and the like, and yields were within normal experimental ranges. In repeated Examples where significant modifications were made, these have been noted where the results varied significantly from those described. In Examples where different starting materials were used, these are noted. When the repeated Examples refer to a "corresponding" analog of a compound, such as a "corresponding ethyl ester", this intends that an otherwise present group, in this case typically a methyl ester, is taken to be the same group modified as indicated.

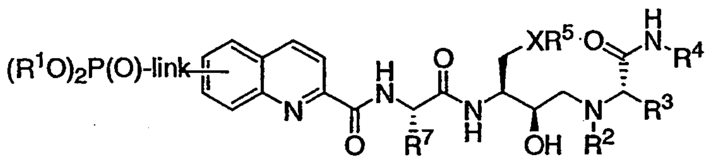
In a number of the following schemes, the term "etc" appears as a substituent on chemical structures and as a term within the schemes. When used in the charts, the term is defined for each chart. When the term "etc" appears in a scheme and is not a substituent on a chemical structure, it means "and the like".

Saquinavir-like phosphonate protease inhibitors (SLPPI)

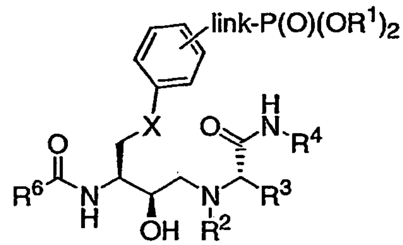
Preparation of the intermediate phosphonate esters.

The structures of the intermediate phosphonate esters **1** to **6**, and the structures for the component groups R^1, R^4 and R^7 of this invention are shown in Chart **1**.
The structures of the $R^2NHCH(R^3)CONHR^4$ and R^5XCH_2 components are shown in Charts **2** and **2a**, and the structures of the R^6COOH components are shown in Charts **3a, 3b** and **3c.** Specific stereoisomers of some of the structures are shown in Charts **1, 2** and **3**; however, all stereoisomers are utilized in the syntheses of the compounds **1** to **6**. Subsequent chemical modifications to the compounds **1** to **6**, as described herein, permit the synthesis of the final compounds of this invention.
The intermediate compounds **1** to **6** incorporate a phosphonate moiety $(R^1O)_2P(O)$ connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures. Charts **4** and **5** illustrate examples of the linking groups present in the structures **1** – **5**, and in which "etc" refers to the scaffold, e.g., saquinavir.

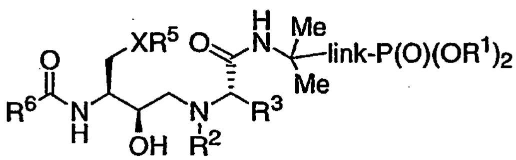
Chart 1



1



2



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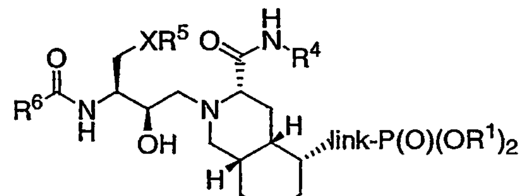
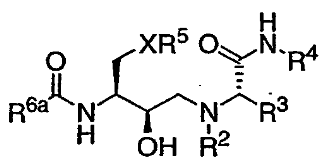
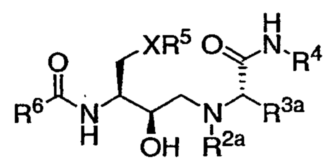


4



5

R^{6a} = phosphonate-containing R^6



6

R^{2a}, R^{3a} = phosphonate-containing R^2 or R^3

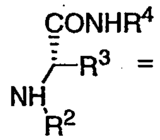
R^1 = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl

R^4 = $CH(CH_3)_3$; CH_2CF_3; $CH_2C_6H_4(CH_3)$-2

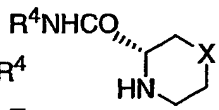
R^7 = alkyl, $CH_2SO_2CH_3$,$C(CH_3)_2SO_2CH_3$,CH_2CONH_2, CH_2SCH_3, imidaz-4-ylmethyl, CH_2NHAc, $CH_2NHCOCF_3$

X = S, direct bond

Chart 2

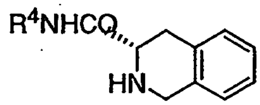


1.2

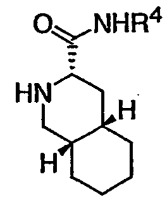


X = NH,CH$_2$

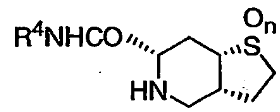
A1



A2

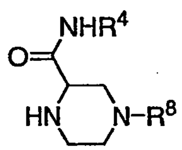


A3

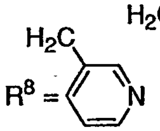


n=0,2

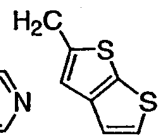
A4



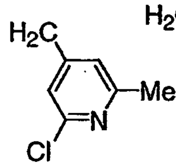
A5



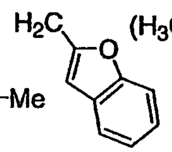
A6



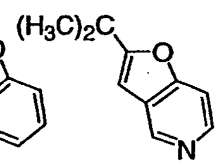
A7



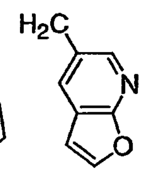
A8



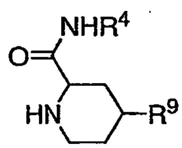
A9



A10

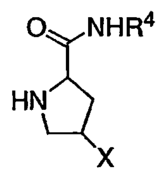


A11

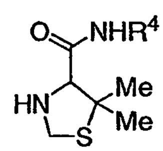


A12

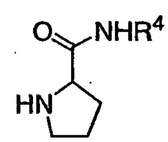
R^9=OCH$_2$Ph
S-3-pyridyl
S-4-pyridyl
OCH$_2$-4-pyridyl



A13

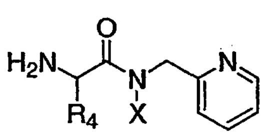


A14



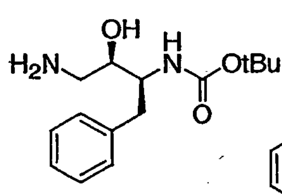
A15

X = Cl, OMe



X=H or Me

A16



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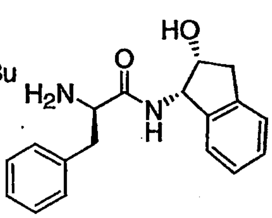

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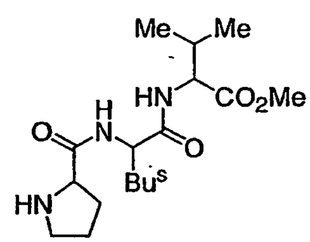

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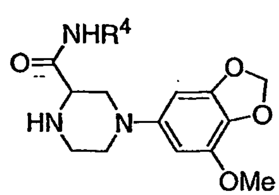
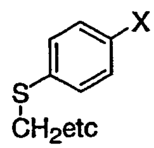


A20

Chart 2a

R^5CH_2X =



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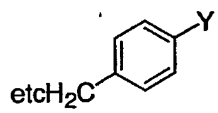

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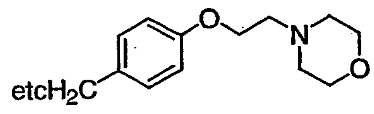
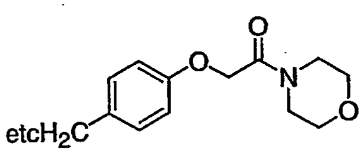


23

X = H, F

Y = H, OC_2H_5, $OCH_2C_6H_5$



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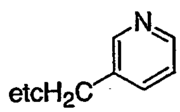

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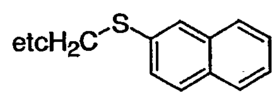
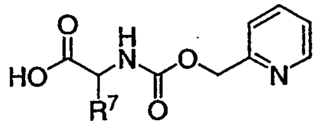
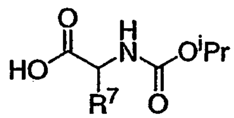


26

Chart 3a Structures of the R^6COOH components



C1



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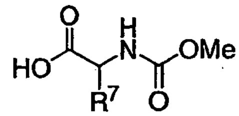
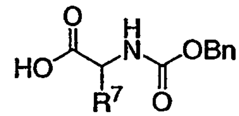


C3



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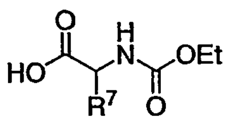

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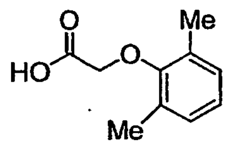
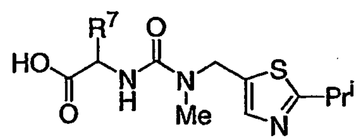


C6



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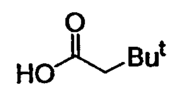

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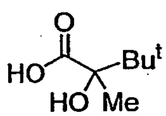

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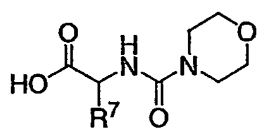

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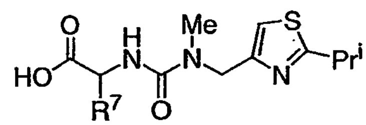

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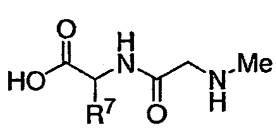

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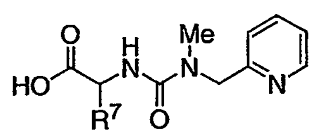

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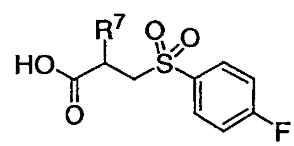

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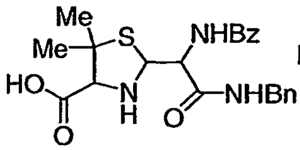

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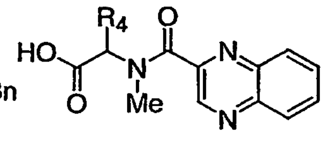

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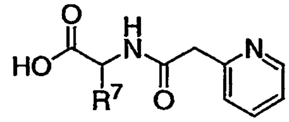

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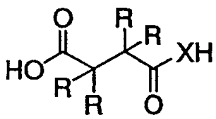
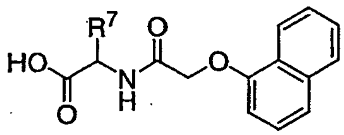


X = O, NH
R = H, alkyl
C18



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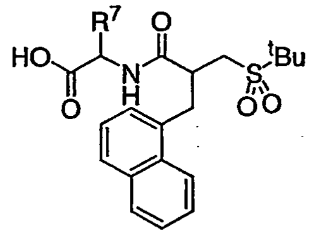

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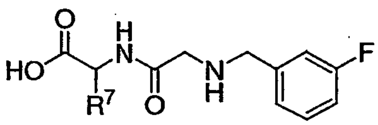

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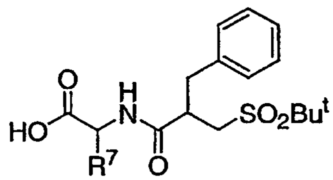

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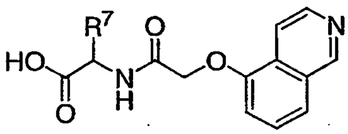

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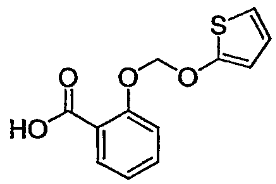
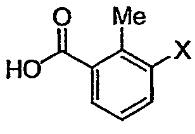


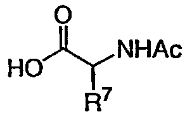
C24

R^7 = alkyl, $CH_2SO_2CH_3$,$C(CH_3)_2SO_2CH_3$,CH_2CONH_2, CH_2SCH_3, imidaz-4-ylmethyl, CH_2NHAc, $CH_2NHCOCF_3$

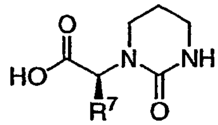
Chart 3b Structures of the R^6COOH components



C25
X = OH, NH_2



C26



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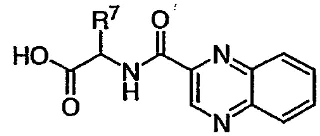

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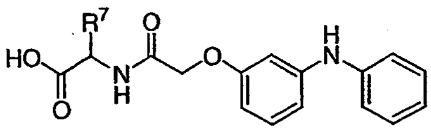

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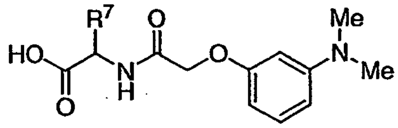

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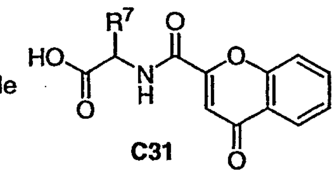

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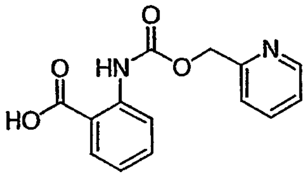

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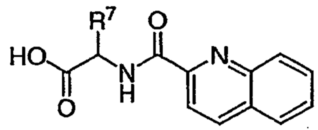

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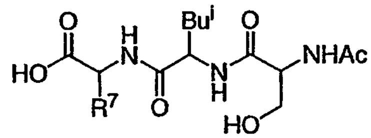

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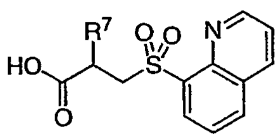

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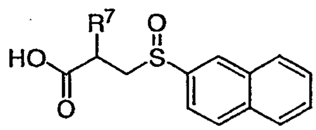

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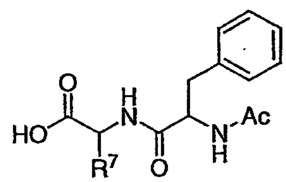

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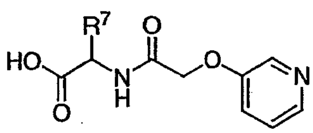
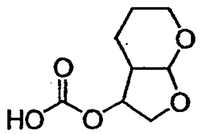


C38

R^7 = alkyl, $CH_2SO_2CH_3$,$C(CH_3)_2SO_2CH_3$,CH_2CONH_2, CH_2SCH_3, imidaz-4-ylmethyl, CH_2NHAc, $CH_2NHCOCF_3$

Chart 3c Structures of the R^{6}COOH components



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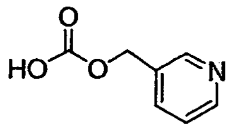

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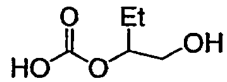

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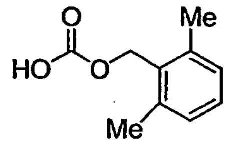

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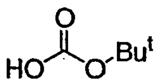

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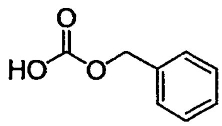

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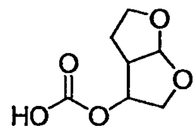

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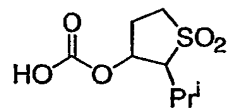

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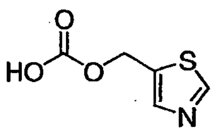

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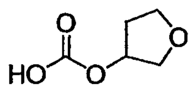

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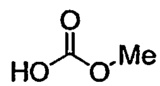

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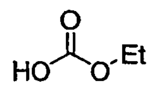
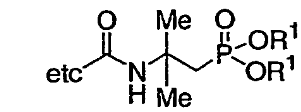


C49

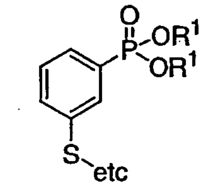
Chart 4 Examples of the linking group between the scaffold and the phosphonate moiety.

link **examples**

direct bond



38



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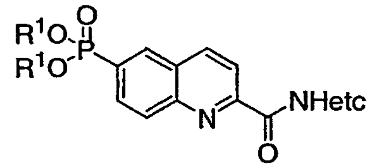
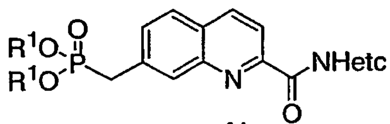


40

single carbon



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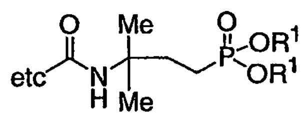

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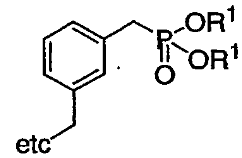
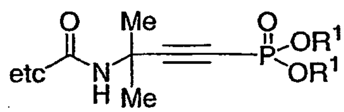


43

multiple carbon



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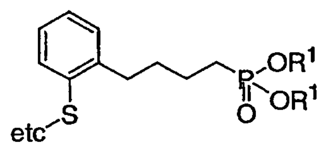

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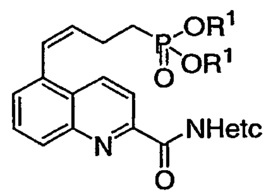
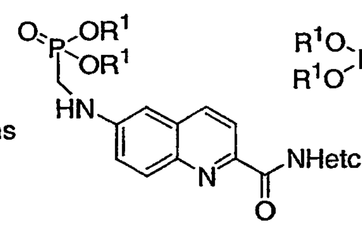


46

hetero atoms



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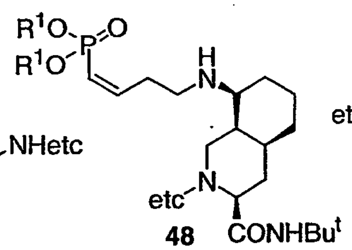

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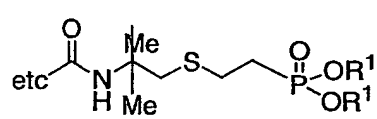

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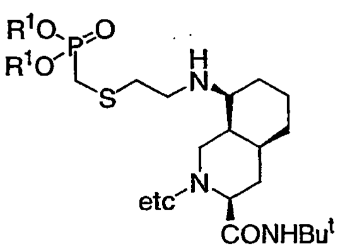

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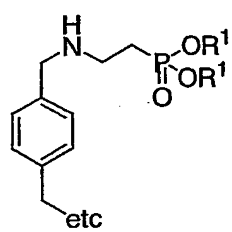

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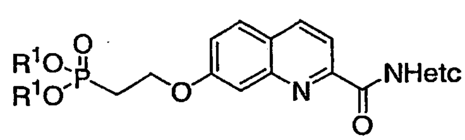
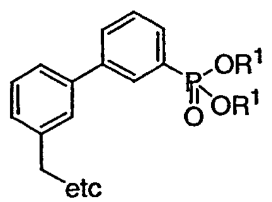


52

Chart 5 Examples of the linking group between the scaffold and the phosphonate moiety.

link	examples

aryl, heteroaryl



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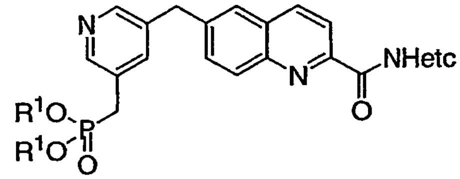
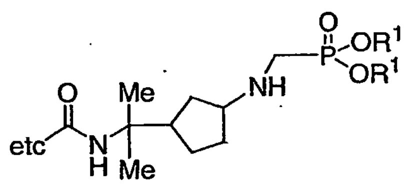


55

cycloalkyl



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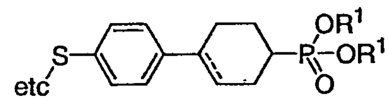
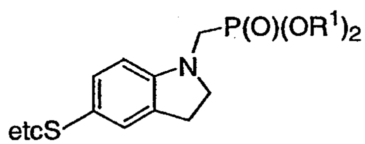


57

cyclized



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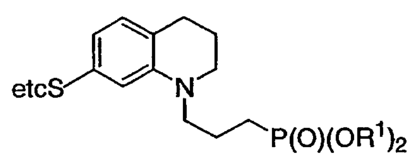

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Schemes **1** - **69** illustrate the syntheses of the intermediate phosphonate compounds of this invention, **1**- **4**, and of the intermediate compounds necessary for their synthesis. The preparation of the phosphonate esters **5** and **6**, in which the phosphonate moiety is incorporated into the groups R^6COOH and $R^2NHCH(R^3)CONHR^4$, are also described below.

Protection of reactive substituents.

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the

art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH].

Preparation of the phosphonate intermediates 1.

Scheme **1** illustrates one method for the preparation of the phosphonate esters **1.6** in which X is a direct bond. In this procedure, an amine $R^2NHCH(R^3)CONHR^4$ **1.2** is reacted with an epoxide **1.1** to afford the aminoalcohol **1.3**. The preparation of the epoxide **1.1** is described below, (Scheme **2**) The preparation of aminoalcohols by reaction between an amine and an epoxide is described, for example, in Advanced Organic Chemistry, by J. March, McGraw Hill, 1968, p 334. In a typical procedure, equimolar amounts of the reactants are combined in a polar solvent such as an alcohol or dimethylformamide and the like, at from ambient to about 100°, for from 1 to 24 hours, to afford the product **1.3**. The carbobenzyloxy protecting group is then removed. The removal of carbobenzyloxy protecting groups is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 335. The reaction can be effected by means of catalytic hydrogenation in the presence of hydrogen or a hydrogen donor, by reaction with a Lewis acid such as aluminum chloride or boron tribromide, or by basic hydrolysis, for example employing barium hydroxide in an aqueous organic solvent mixture. Preferably, the protected amine **1.3** is converted into the free amine **1.4** by means of hydrogenation over 10% palladium on carbon catalyst in ethanol, as described in US Patent 5196438. The amine product **1.4** is then reacted with a carboxylic acid **1.5** to afford the amide **1.6**. The coupling reaction of amines **1.4** and a carboxylic acid **1.5** can be effected under a variety of conditions, for example as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 972ff. The carboxylic acid can be activated by conversion to an imidazolide, mixed anhydride or active ester such as, for example, the ester with hydroxybenztriazole or N-hydroxysuccinimide. Alternatively, the reactants can be combined in the presence of a carbodiimide, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, to afford the amide product **1.6**. Preferably, equimolar amounts of the amine and the carboxylic acid are reacted in tetrahydrofuran at ca. -10°, in the presence of dicyclohexylcarbodiimide, as described in

U.S. Patent 5,196,438, to afford the amide **1.6**. The carboxylic acid **1.5** employed in the above reaction is obtained by means of the reaction between the substituted quinoline-2-carboxylic acid **1.7**, in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor group thereto, such as [OH], [SH], Br, as described below, and an aminoacid **1.8**. The reaction is performed under similar conditions to those described above for the preparation of the amide **1.6**. Preferably, the quinoline carboxylic acid **1.7** is reacted with N-hydroxy succinimide and a carbodiimide to afford the hydroxysuccinimide ester, which is then reacted with the aminoacid **1.8** in dimethylformamide at ambient temperature for 2-4 days, as described in U.S. Patent 5,196,438, to afford the amide product **1.5**. The preparation of the substituted quinoline carboxylic acids **1.7** is described below, Schemes **24-27**.

Scheme **2** illustrates the preparation of the epoxides **1.1** used above in Scheme **1**. The preparation of the epoxide **1.1** in which R10 is H is described in J. Med. Chem., 1997, 40, 3979. Analogs in which R10 is one of the substituents defined in Chart **2** are prepared as shown in Scheme **2**. A substituted phenylalanine **2.1** is first converted into the benzyloxycarbonyl derivative **2.2**. The preparation of benzyloxycarbonyl amines is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 335. The aminoacid **2.1** is reacted with benzyl chloroformate or dibenzyl carbonate in the presence of a suitable base such as sodium carbonate or triethylamine, to afford the protected amine product **2.2**. The conversion of the carboxylic acid **2.2** into the epoxide **1.1** for example using the sequence of reactions which is described in J. Med. Chem., 1994, 37, 1758, is then effected. The carboxylic acid is first converted into an activated derivative such as the acid chloride **2.3**, in which X is Cl, for example by treatment with oxalyl chloride, or into a mixed carbonate, for example by treatment with isobutyl chloroformate, and the activated derivative thus obtained is reacted with ethereal diazomethane, to afford the diazoketone **2.4**. The reaction is performed by the addition of a solution of the activated carboxylic acid derivative to an ethereal solution of three or more molar equivalents of diazomethane at 0°C. The diazoketone is converted into the chloroketone **2.5** by reaction with anhydrous hydrogen chloride, in a suitable solvent such as diethyl ether, as described in J. Med. Chem., 1997, 40, 3979. The latter compound is then reduced, for example by the use of an equimolar amount of sodium borohydride in an ethereal solvent such as tetrahydrofuran at 0°C, to produce a mixture of chlorohydrins from which the desired 2S, 3S diastereomer **2.6** is

separated by chromatography. The chlorohydrin **2.6** is then converted into the epoxide **1.1** by treatment with a base such as an alkali metal hydroxide in an alcoholic solvent, for example as described in J. Med. Chem., 1997, 40, 3979. Preferably, the compound **2.6** is reacted with ethanolic potassium hydroxide at ambient temperature to afford the epoxide **1.1**.

Scheme **3** illustrates the preparation of the amine reactant $R^2NHCH(R^3)CONHR^4$ (**1.2**) employed above (Scheme **1**). In this procedure, the carboxylic acid $R^2NHCH(R^3)COOH$ **3.1** is first converted into the N-protected analog **3.2**, for example by reaction with benzyloxychloroformate and triethylamine in tetrahydrofuran. The carboxyl group is then activated, for example by conversion to the acid chloride or a mixed anhydride, or by reaction with isobutyl chloroformate, as described in Chimia, 50, 532, 1996 and in Synthesis, 1972, 453, and the activated derivative is then reacted with the amine R^4NH_2 to produce the amide **3.4**. Deprotection, for example as described above, then affords the free amine **1.2**.

Scheme **4** depicts an alternative method for the preparation of the compounds **1** in which X is a direct bond. In this procedure, a hydroxymethyl-substituted oxazolidinone **4.1** is converted into an activated derivative **4.2** which is then reacted with the amine $R^2NHCH(R^3)CONHR^4$ (**1.2**) to afford the amide **4.3**. The preparation of the hydroxymethyl-substituted oxazolidinone **4.1** is described below, (Scheme **5**) The hydroxyl group can be converted into a bromo derivative, for example by reaction with triphenylphosphine and carbon tetrabromide, as described in J. Am. Chem. Soc., 92, 2139, 1970, or a methanesulfonyloxy derivative, by reaction with methanesulfonyl chloride and a base, or, preferably, into the 4-nitrobenzenesulfonyloxy derivative **4.2**, by reaction in a solvent such as ethyl acetate or tetrahydrofuran, with 4-nitrobenzenesulfonyl chloride and a base such as triethylamine or N-methylmorpholine, as described in WO 9607642. The nosylate product **4.2** is then reacted with the amine component **1.2** to afford the displacement product **4.3**. Equimolar amounts of the reactants are combined in an inert solvent such as dimethylformamide, acetonitrile or acetone, optionally in the presence of an organic or inorganic base such as triethylamine or sodium carbonate, at from about 0°C to 100°C to afford the amine product **4.3**. Preferably, the reaction is performed in methyl isobutyl ketone at 80°C, in the presence of sodium carbonate, as described in WO 9607642. The oxazolidinone group present in the product **4.3** is then hydrolyzed to afford the hydroxyamine **4.4**. The hydrolysis reaction is effected in the presence

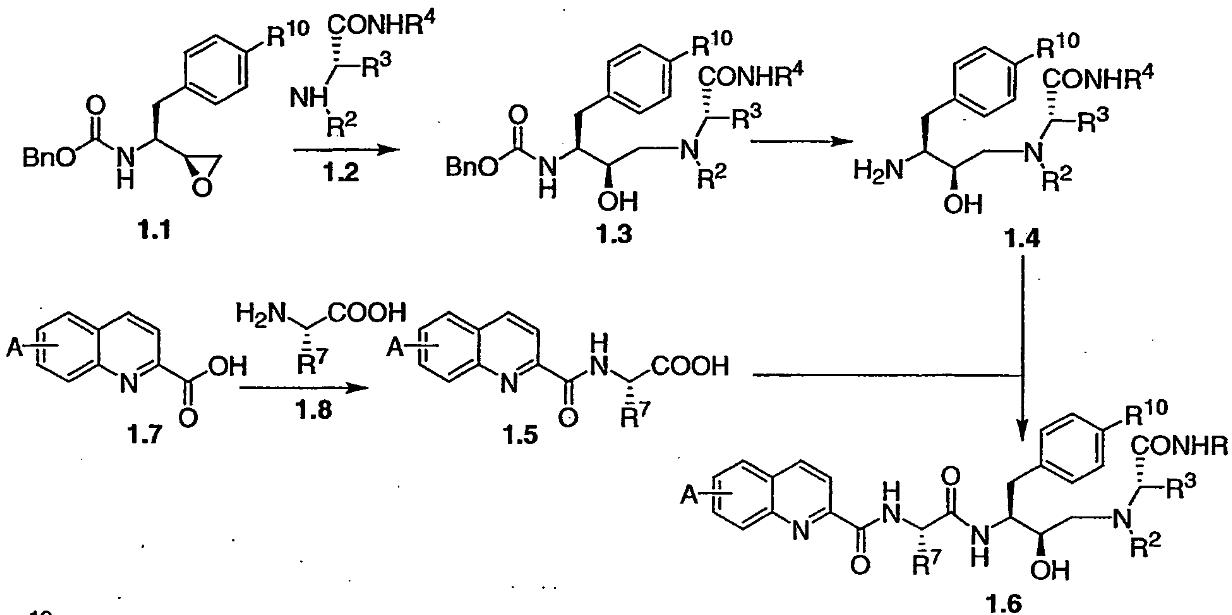
of aqueous solution of a base such as an alkali metal hydroxide, optionally in the presence of an organic co-solvent. Preferably, the oxazolidinone compound **4.3** is reacted with aqueous ethanolic sodium hydroxide at reflux temperature, as described in WO 9607642, to afford the amine **4.4**. This product is then reacted with the carboxylic acid or activated derivative thereof, **1.5**, the preparation of which is described above, to afford the product **1.6**. The amide-forming reaction is conducted under the same conditions as described above, (Scheme **1**)

Scheme **5** depicts the preparation of the hydroxymethyl oxazolidinones **4.1**, which are utilized in the preparation of the phosphonate esters **1**, as described above in Scheme **4**. In this procedure, phenylalanine, or a substituted derivative thereof, **2.1**, in which R^{10} is as defined in Chart **2**, is converted into the phthalimido derivative **5.1**. The conversion of amines into phthalimido derivatives is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 358. The amine is reacted with phthalic anhydride, 2-carboethoxybenzoyl chloride or N-carboethoxyphthalimide, optionally in the presence of a base such as triethylamine or sodium carbonate, to afford the protected amine **5.1**. Preferably, the aminoacid is reacted with phthalic anhydride in toluene at reflux, to yield the phthalimido product. The carboxylic acid is then transformed into an activated derivative such as the acid chloride **5.2**, in which X is Cl. The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane, optionally in the presence of a catalytic amount of a tertiary amide such as dimethylformamide. Preferably, the carboxylic acid is transformed into the acid chloride by reaction with oxalyl chloride and a catalytic amount of dimethylformamide, in toluene solution at ambient temperature, as described in WO 9607642. The acid chloride **5.2**, X = Cl, is then converted into the aldehyde **5.3** by means of a reduction reaction. This procedure is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 620. The transformation can be effected by means of catalytic hydrogenation, a procedure which is referred to as the Rosenmund reaction, or by chemical reduction employing, for example, sodium borohydride, lithium aluminum tri-tertiarybutoxy hydride or triethylsilane. Preferably, the acid chloride **5.2** X = Cl, is hydrogenated in toluene solution over a 5% palladium on carbon catalyst, in the presence of

butylene oxide, as described in WO 9607642, to afford the aldehyde **5.3**. The aldehyde **5.3** is then transformed into the cyanohydrin derivative **5.4**. The conversion of aldehydes into cyanohydrins is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 211. For example, the aldehyde **5.3** is converted into the cyanohydrin **5.4** by reaction with trimethylsilyl cyanide in an inert solvent such as dichloromethane, followed by treatment with an organic acid such as citric acid, as described in WO 9607642, or by alternative methods described therein. The cyanohydrin is then subjected to acidic hydrolysis, to effect conversion of the cyano group into the corresponding carboxy group, with concomitant hydrolysis of the phthalimido substituent to afford the aminoacid **5.5** The hydrolysis reactions are effected by the use of aqueous mineral acid. For example, the substrate **5.4** is reacted with aqueous hydrochloric acid at reflux, as described in WO 9607642, to afford the carboxylic acid product **5.5**. The aminoacid is then converted into a carbamate, for example the ethyl carbamate **5.6**. The conversion of amines into carbamates is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 317. The amine is reacted with a chloroformate, for example ethyl chloroformate, in the presence of a base such as potassium carbonate, to afford the carbamate **5.6**. For example, the aminoacid **5.5** is reacted, in aqueous solution, with ethyl chloroformate and sufficient aqueous sodium hydroxide to maintain a neutral pH, as described in WO 9607642, to afford the carbamate **5.6**. The latter compound is then transformed into the oxazolidinone **5.7**, for example by treatment with aqueous sodium hydroxide at ambient temperature, as described in WP 9607642. The resultant carboxylic acid is transformed into the methyl ester **5.8** by means of a conventional esterification reaction. The conversion of carboxylic acids into esters is described for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 966. The conversion can be effected by means of an acid-catalyzed reaction between the carboxylic acid and an alcohol, or by means of a base-catalyzed reaction between the carboxylic acid and an alkyl halide, for example an alkyl bromide. For example, the carboxylic acid **5.7** is converted into the methyl ester **5.8** by treatment with methanol at reflux temperature, in the presence of a catalytic amount of sulfuric acid, as described in WO 9607642. The carbomethoxyl group present in the compound **5.8** is then reduced to yield the corresponding carbinol **4.1**. The reduction of carboxylic esters to the carbinols is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 550. The transformation can be effected by the use of reducing agents such as

borane-dimethylsulfide, lithium borohydride, diisobutyl aluminum hydride, lithium aluminum hydride and the like. For example, the ester **5.8** is reduced to the carbinol **4.1** by reaction with sodium borohydride in ethanol at ambient temperature, as described in WO 9607642.

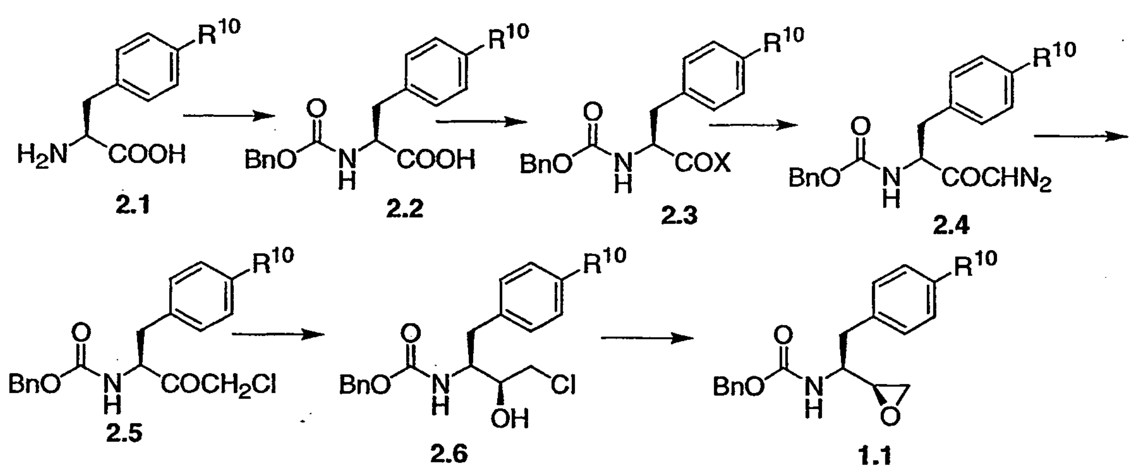
Scheme 1



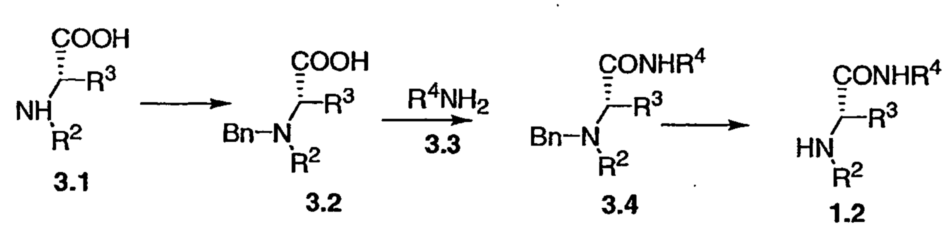
R^{10} = H, OC_2H_5, $OCH_2C_6H_5$, OCH_2CH_2morpholino, OCH_2COmorpholino

A = [OH], [SH], [NH_2], Br etc or link-$P(O)(OR^1)_2$

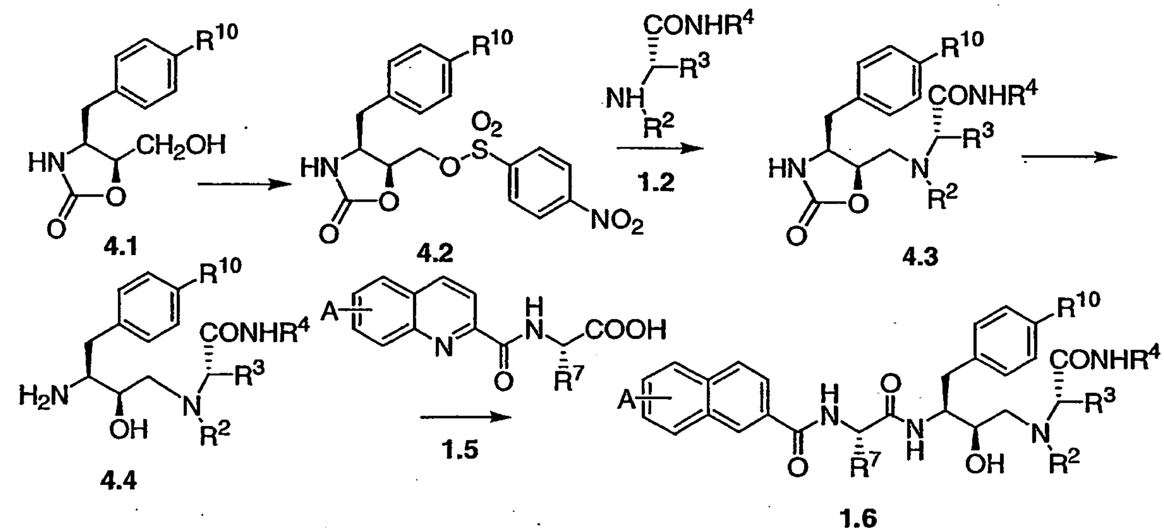
Scheme 2



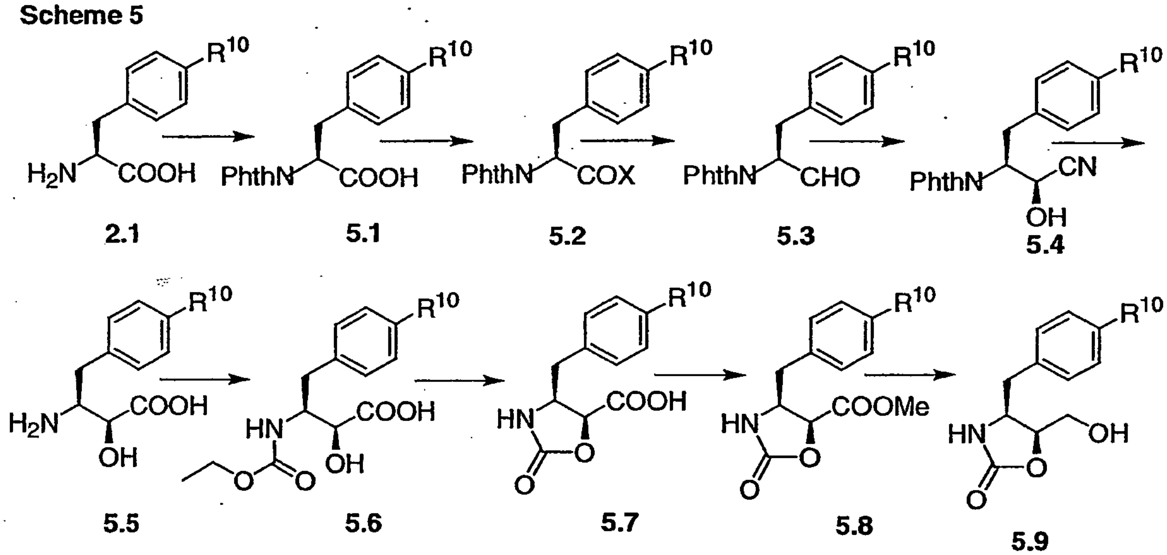
Scheme 3



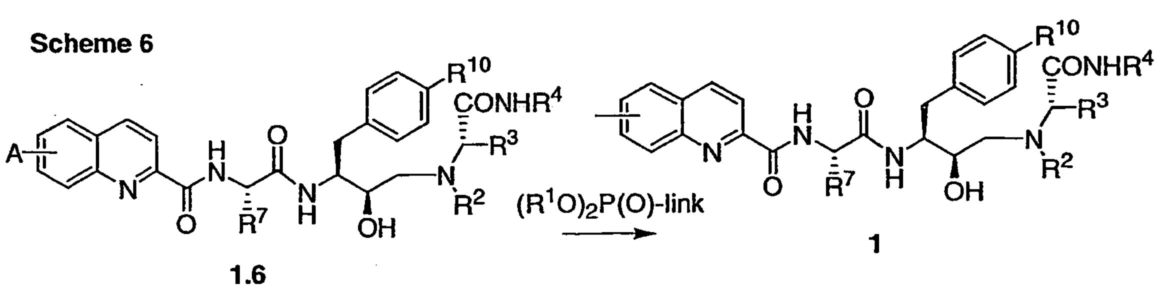
Scheme 4



Scheme 5

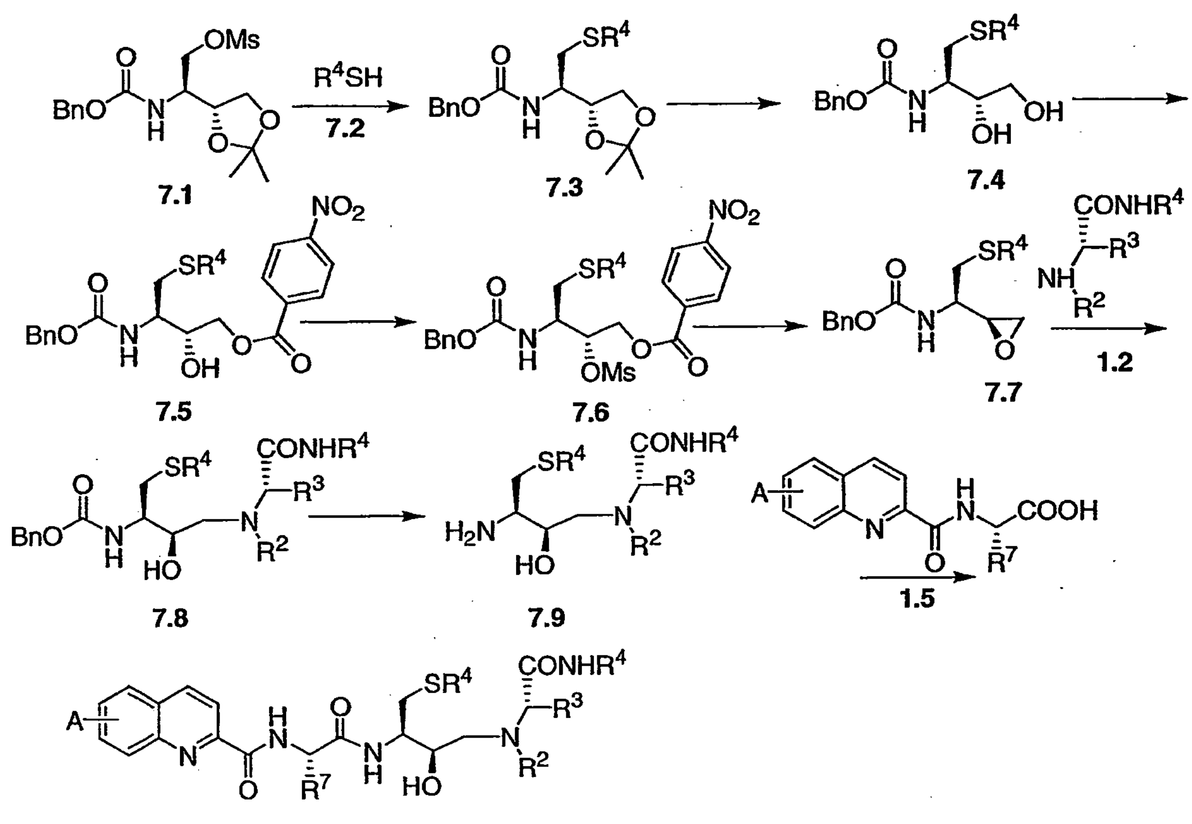


Scheme 6



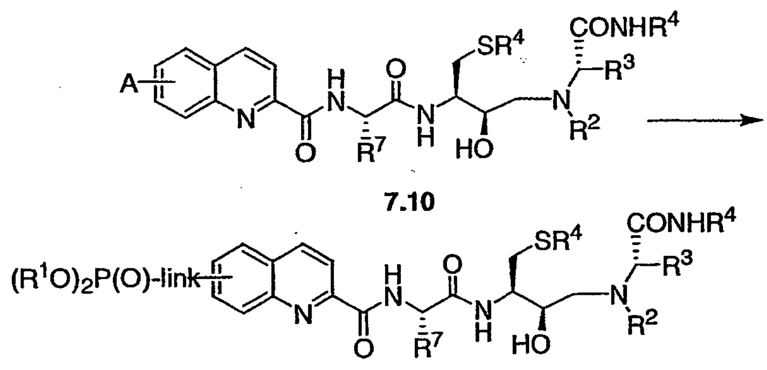
The procedures illustrated in Schemes **1** and **4** depict the preparation of the compounds **1.6** in which X is a direct bond, and in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme **6** illustrates the conversion of compounds **1.6** in which A is a precursor to the group link-$P(O)(OR^1)_2$ into the compounds **1**. Procedures for the conversion of the substituent A into the group link-$P(O)(OR^1)_2$ are illustrated below, (Schemes **24 - 69**). In the procedures illustrated above, Schemes **1, 4** and in the procedures illustrated below (Schemes **24-69**) for the preparation of the phosphonate esters **2-6**, compounds in which the group A is a precursor to the group link-$P(O)(OR^1)_2$ may be converted into compounds in which A is link-$P(O)(OR^1)_2$ at any appropriate stage in the reaction sequence, or, as shown in Scheme **6**, at the end of the sequence. The selection of an appropriate stage to effect the conversion of the group A into the group link-$P(O)(OR^1)_2$ is made after consideration of the nature of the reactions involved in the conversion, and the stability of the various components of the substrate to those conditions.

Scheme 7



7.10 $R^4SH = C_6H_5SH$, 4-FC_6H_5SH, 2-naphthyl-SH

Scheme 8



1

Scheme 7 illustrates the preparation of the compounds **1** in which the substituent X is S, and in which the group A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below.

In this sequence, methanesulfonic acid 2-benzoyloxycarbonylamino-2-(2,2-dimethyl-[1,3]dioxolan-4-yl)-ethyl ester, **7.1**, prepared as described in J. Org. Chem, 2000, 65, 1623, is reacted with a thiol R^4SH **7.2**, as defined above, to afford the thioether **7.3**.

The reaction is conducted in a suitable solvent such as, for example, pyridine, DMF and the like, in the presence of an inorganic or organic base, at from 0°C to 80°C, for from 1-12 hours, to afford the thioether **7.3**. Preferably the mesylate **7.1** is reacted with an equimolar amount of the thiol R^4SH, in a mixture of a water-immiscible organic solvent such as toluene, and water, in the presence of a phase-transfer catalyst such as, for example, tetrabutyl ammonium bromide, and an inorganic base such as sodium hydroxide, at about 50°C, to give the product **7.3**. The 1,3-dioxolane protecting group present in the compound **7.3** is then removed by acid catalyzed hydrolysis or by exchange with a reactive carbonyl compound to afford the diol **7.4**. Methods for conversion of 1,3-dioxolanes to the corresponding diols are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition 1990, p. 191. For example, the 1,3-dioxolane compound **7.3** is hydrolyzed by reaction with a catalytic amount of an acid in an aqueous organic solvent mixture. Preferably, the 1,3-dioxolane **7.3** is dissolved in aqueous methanol containing hydrochloric acid, and heated at ca. 50°C, to yield the product **7.4**.

The primary hydroxyl group of the diol **7.4** is then selectively acylated by reaction with an electron-withdrawing acyl halide such as, for example, pentafluorobenzoyl chloride or mono- or di-nitrobenzoyl chlorides. The reaction is conducted in an inert solvent such as dichloromethane and the like, in the presence of an inorganic or organic base.

Preferably, equimolar amounts of the diol **7.4** and 4-nitrobenzoyl chloride are reacted in a solvent such as ethyl acetate, in the presence of a tertiary organic base such as 2-picoline, at ambient temperature, to afford the hydroxy ester **7.5**. The hydroxy ester is next reacted with a sulfonyl chloride such as methanesulfonyl chloride, 4-toluenesulfonyl chloride and the like, in the presence of a base, in an aprotic polar solvent at low temperature, to afford the corresponding sulfonyl ester **7.6**. Preferably, equimolar amounts of the carbinol **7.5** and methanesulfonyl chloride are reacted together in ethyl acetate containing triethylamine, at about 10°C, to yield the mesylate **7.6**. The compound **7.6** is then subjected to a hydrolysis-cyclization reaction to afford the oxirane **7.7**. The mesylate or analogous leaving group present in **7.6** is displaced by hydroxide ion, and the carbinol thus produced, without isolation, spontaneously transforms into the oxirane **7.7** with elimination of 4-nitrobenzoate. To effect

this transformation, the sulfonyl ester **7.6** is reacted with an alkali metal hydroxide or tetraalkylammonium hydroxide in an aqueous organic solvent. Preferably, the mesylate **7.6** is reacted with potassium hydroxide in aqueous dioxan at ambient temperature for about 1 hour, to afford the oxirane **7.7**.

The oxirane compound **7.7** is then subjected to regiospecific ring-opening reaction by treatment with a secondary amine **1.2**, to give the aminoalcohol **7.8**. The amine and the oxirane are reacted in a protic organic solvent, optionally in the additional presence of water, at 0°C to 100°C, and in the presence of an inorganic base, for 1 to 12 hours, to give the product **7.8**. Preferably, equimolar amounts of the reactants **7.7** and **1.2** are reacted in aqueous methanol at about 60°C in the presence of potassium carbonate, for about 6 hours, to afford the aminoalcohol **7.8**. The carbobenzyloxy (cbz) protecting group in the product **7.8** is removed to afford the free amine **7.9**. Methods for removal of cbz groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition, p. 335. The methods include catalytic hydrogenation and acidic or basic hydrolysis.

For example, the cbz-protected amine **7.8** is reacted with an alkali metal or alkaline earth hydroxide in an aqueous organic or alcoholic solvent, to yield the free amine **7.9**. Preferably, the cbz group is removed by the reaction of **7.8** with potassium hydroxide in an alcohol such as isopropanol at ca. 60°C to afford the amine **7.9**. The amine **7.9** so obtained is next acylated with a carboxylic acid or activated derivative **1.5**, using the conditions described above for the conversion of the amine **1.4** into the amide **1.6** (Scheme **1**), to yield the final amide product **7.10**.

The procedures illustrated in Scheme **7** depict the preparation of the compounds **1** in which X is S, and in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor thereto, such as [OH], [SH] Br , as described below. Scheme **8** illustrates the conversion of compounds **7.10** in which A is a precursor to the group link-P(O)(OR^1)$_2$ into the compounds **1**. Procedures for the conversion of the substituent A into the group link-P(O)(OR^1)$_2$ are illustrated below, (Schemes **24 - 69**).

The reactions illustrated in Schemes **1-7** illustrate the preparation of the compounds **1** in which A is either the group link-P(O)(OR^1)$_2$ or a precursor thereto, such as, for example, optionally protected OH, SH, NH , as described below. Scheme **8** depicts the conversion of the

compounds **1** in which A is OH, SH, NH , as described below, into the compounds **1** in which A is the group link-P(O)(OR^1)$_2$. Procedures for the conversion of the group A into the group link-P(O))(OR^1)$_2$ are described below, (Schemes **24-69**).

In this and succeeding examples, the nature of the phosphonate ester group can be varied, either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described below, (Scheme **54**)

Preparation of the phosphonate intermediates 2.

Scheme **9** depicts the one method for the preparation of the compounds **2** in which X is a direct bond, and in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. In this procedure, the hydroxymethyl oxazolidinone **9.1**, the preparation of which is described below, is converted into an activated derivative, for example the 4-nitrobenzenesulfonate **9.2**. The conditions for this transformation are the same as those described above (Scheme **4**) for the conversion of the carbinol **4.1** into the nosylate **4.2**. The activated ester **9.2** is then reacted with the amine **1.2**, under the same conditions as described above for the preparation of the amine **4.3** to afford the oxazolidinone amine **9.3**. The oxazolidinone group is then hydrolyzed by treatment with aqueous alcoholic base, to produce the primary amine **4.4**. For example, the oxazolidinone **9.3** is reacted with aqueous ethanolic sodium hydroxide at reflux temperature, as described in WO 9607642, to afford the amine product **9.4**. The latter compound is then coupled with the carboxylic acid **9.6**, to afford the amide **9.5**. The conditions for the coupling reaction are the same as those described above for the preparation of the amide **1.6**.

The phosphonate esters **2 - 6** which incorporate the group R^6 CO derived formally from the carboxylic acids depicted in Chart **2c** contain a carbamate group. Various methods for the preparation of carbamates are described below, (Scheme **55**)

Scheme **10** illustrates an alternative method for the preparation of the compounds **2** in which X is a direct bond, and in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. In this procedure, the oxirane **10.1**, the preparation of which is described below, is reacted with the amine **1.2** to afford the

aminoalcohol **10.2**. The reaction is conducted under the same conditions as are described above for the preparation of the aminoalcohol **1.3**. (Scheme **1**) The benzyloxycarbonyl protecting group is then removed from the product **10.2** to afford the free amine **10.3**. The conditions for the debenzylation reaction are the same as those described above for the debenzylation of the compound **1.3**. The amine **10.3** is then coupled with the carboxylic acid **9.6** to produce the amide **9.5**, employing the same conditions as are described above (Scheme **9**).

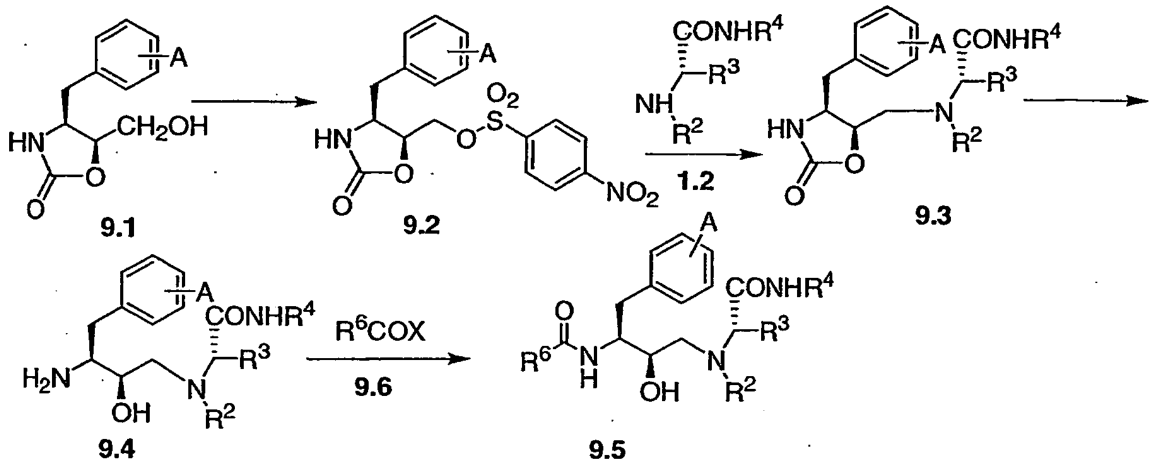
The procedures illustrated in Schemes **9** and **10** depict the preparation of the compounds **9.5** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme **11** illustrates the conversion of compounds **9.5** in which A is a precursor to the group link-$P(O)(OR^1)_2$ into the compounds **2**. Procedures for the conversion of the substituent A into the group link-$P(O)(OR^1)_2$ are illustrated below, (Schemes **24** -**69**).

Schemes **12** and **13** depict the preparation of compounds **2** in which X is sulfur. As shown in Scheme **12**, a substituted thiophenol **12.2**, in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below, is reacted with methanesulfonic acid 2-benzyloxycarbonylamino-2-(2,2-dimethyl-[1,3]dioxolan-4-yl)-ethyl ester **12.1**, the preparation of which is described in J. Org. Chem, 2000, 65, 1623, to afford the displacement product **12.3**. The conditions for the reaction are the same as described above for the preparation of the thioether **7.3**. Methods for the preparation of the substituted thiophenol **12.2** are described below, Schemes **35** - **44**. The thioether product **12.3** is then transformed, using the series of reactions described above, Scheme **7**, for the conversion of the thioether **7.3** into the amine **7.9**. The conditions employed for this series of reactions are the same as those described above, (Scheme **7**). The amine **12.4** is then reacted with the carboxylic acid or activated derivative thereof, **9.6** to afford the amide **12.5**. The conditions for the reaction are he same as those described above for the preparation of the amide **9.5**.

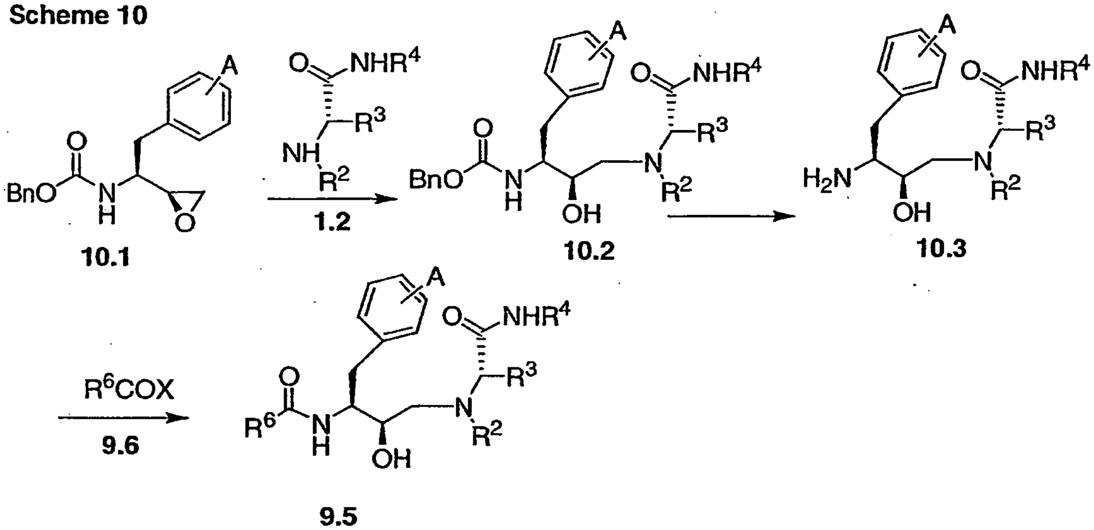
The procedures illustrated in Scheme **12** depict the preparation of the compounds **12.5** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme **13** illustrates the conversion of compounds **12.5**

in which A is a precursor to the group link-$P(O)(OR^1)_2$ into the compounds **2**. Procedures for the conversion of the substituent A into the group link-$P(O)(OR^1)_2$ are illustrated below, (Schemes **24** - **69**).

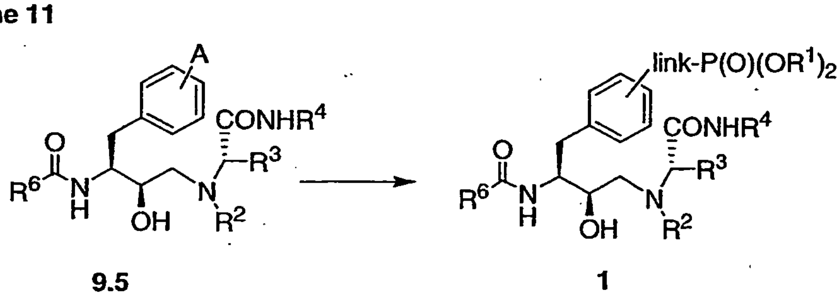
Scheme 9



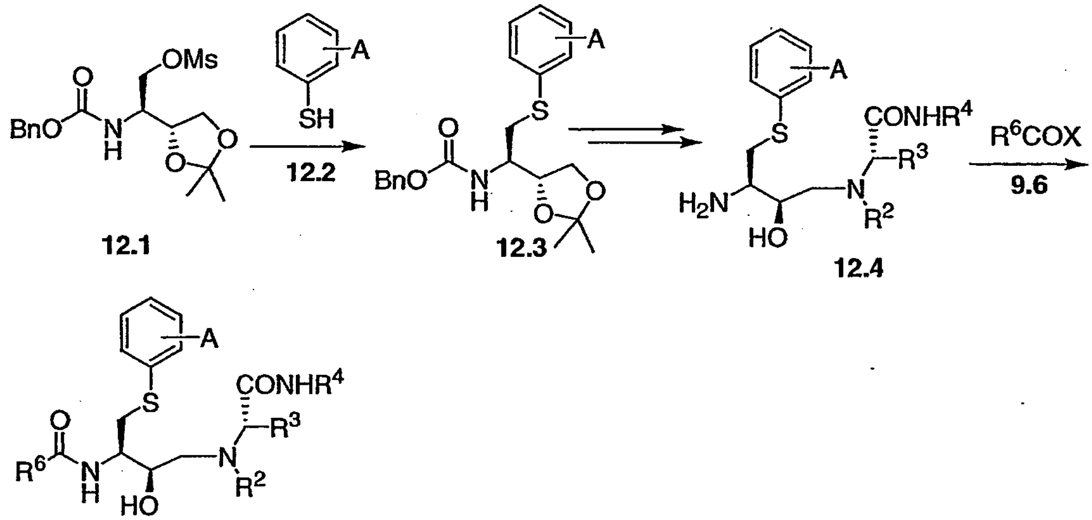
Scheme 10



Scheme 11

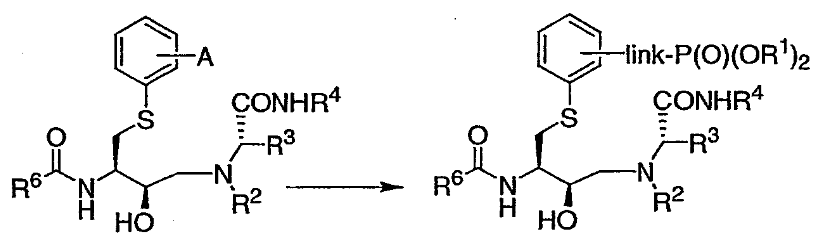


Scheme 12



12.5

Scheme 13



12.5 2

Preparation of the phosphonate intermediates 3.

Schemes **14-16** depict the preparation of the phosphonate esters **3** in which X is a direct bond. As shown in Scheme **14**, the oxirane **1.1**, the preparation of which is described above, is reacted with the amine **14.1** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below, to yield the hydroxyamine **14.2.** The conditions for the reaction are the same as described above for the preparation of the amine **1.3**. Methods for the preparation of the amine **14.1** are described below, Schemes **45** -

48. The hydroxyamine product **14.2** is then deprotected to afford the free amine **14.3**. The conditions for the debenzylation reaction are the same as those described above for the preparation of the amine **1.4**. (Scheme **1**). The amine **14.3** is then coupled with the carboxylic acid or activated derivative thereof, **9.6**, to afford the amide **14.4**, using the conditions described above for the preparation of the amide **12.5**.

Scheme **15** illustrates an alternative method for the preparation of the phosphonate esters **14.4**. In this reaction sequence, the 4-nitrobenzenesulfonate **4.2**, the preparation of which is described above, (Scheme **4**), is reacted with the amine **14.1**, in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below, to yield the amine **15.1**. The reaction is conducted under the same conditions as described above for the preparation of the amide **4.3**. The oxazolidine moiety present in the product is then removed, using the procedure described above for the conversion of the oxazolidine **4.3** into the hydroxyamine **4.4**, to afford the hydroxyamine **15.2**. The latter compound is then coupled, as described above, with the carboxylic acid or activated derivative thereof, **9.6**, to afford the amide **14.4**.

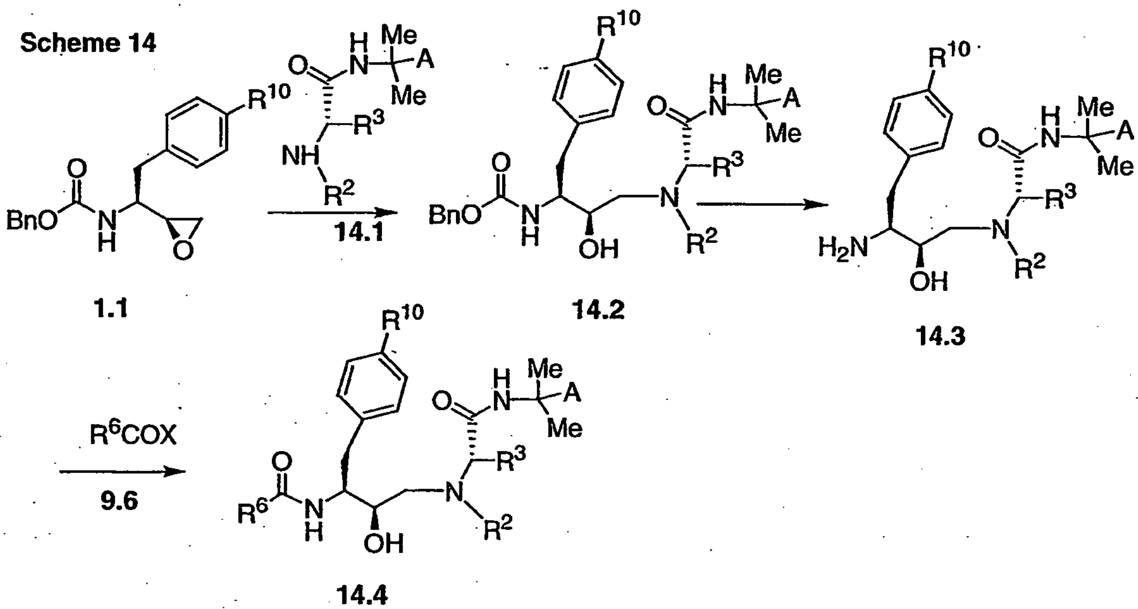
The procedures illustrated in Schemes **14** and **15** depict the preparation of the compounds **14.4** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme **16** illustrates the conversion of compounds **14.4** in which A is a precursor to the group link-$P(O)(OR^1)_2$ into the compounds **3**. Procedures for the conversion of the substituent A into the group link-$P(O)(OR^1)_2$ are illustrated below, (Schemes **24** - **69**).

Schemes **17** and **18** illustrates the preparation of the phosphonate esters **3** in which X is sulfur. As shown in Scheme **17**, the oxirane **7.7**, the preparation of which is described above, (Scheme **7**) is reacted with the amine **14.1**. The conditions for the ring-opening reaction are the same as those described above for the preparation of the aminoalcohol **7.8**, (Scheme **7**). The benzyloxycarbonyl protecting group is then removed to produce the free amine **17.2**. The conditions for the deprotection reaction are the same as those described above for the conversion of the protected amine **7.8** to the amine **7.9** (Scheme **7**) The amine product **17.2** is

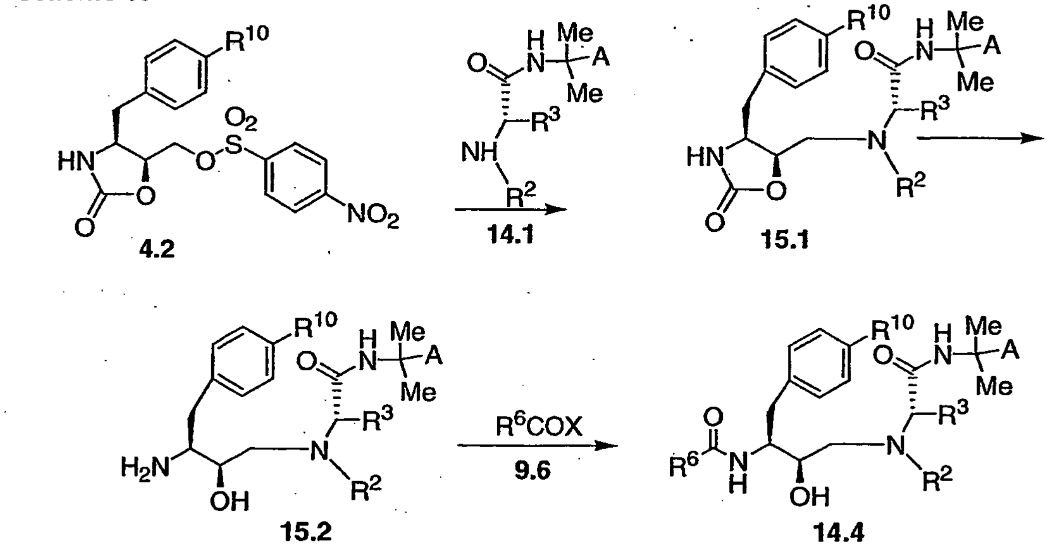
then coupled with the carboxylic acid or activated derivative thereof, **9.6**, using the same conditions as described above, to afford the amide **17.3**.

The procedures illustrated in Scheme **17** depict the preparation of the compound **17.3** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme **18** illustrates the conversion of compounds **17.3** in which A is a precursor to the group link-$P(O)(OR^1)_2$ into the compounds **3**. Procedures for the conversion of the substituent A into the group link-$P(O)(OR^1)_2$ are illustrated below, (Schemes **24** - **69**).

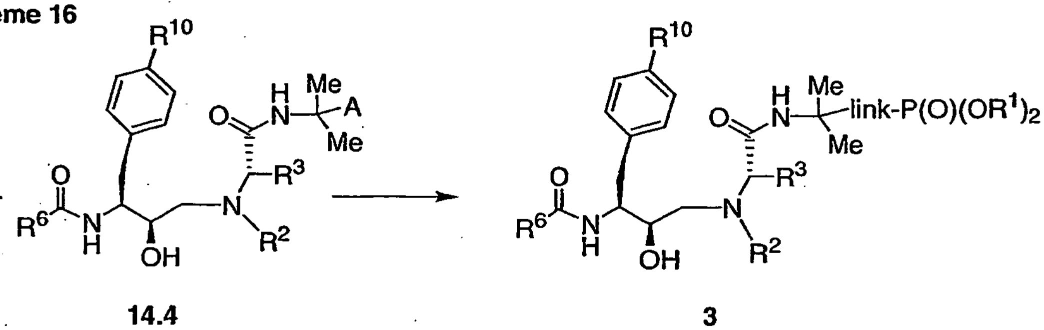
Scheme 14



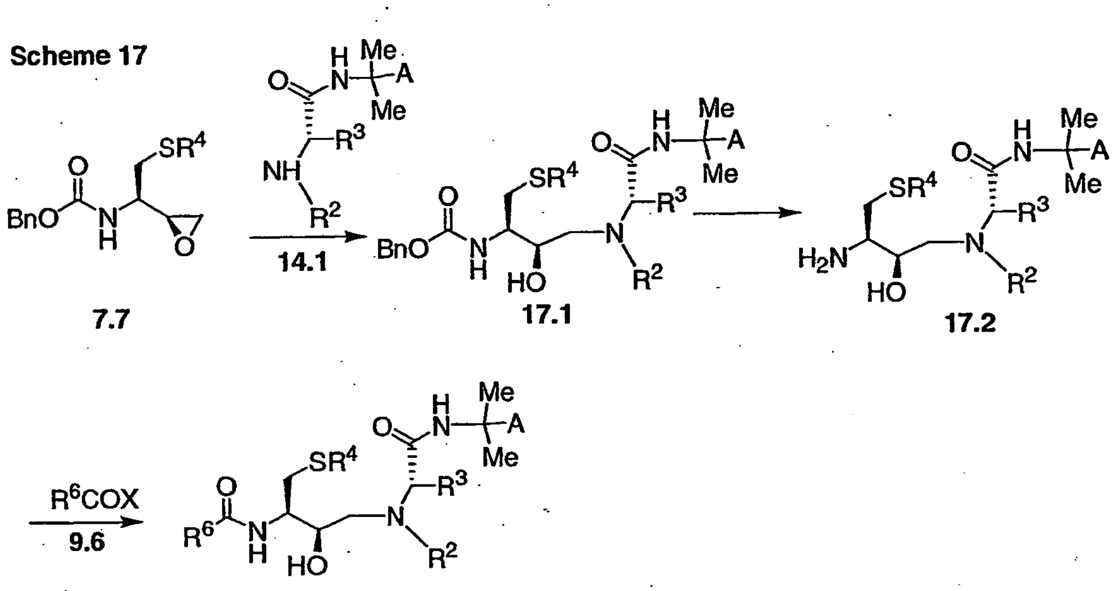
Scheme 15



Scheme 16

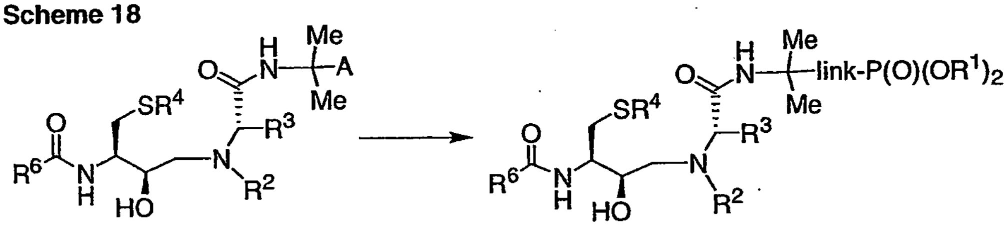


Scheme 17



7.7 17.1 17.2 17.3

Scheme 18



17.3 3

Preparation of the phosphonate intermediates 4.

Scheme **19** illustrates one method for the preparation of the phosphonate esters **4** in which X is a direct bond. In this reaction sequence, the oxirane **1.1**, the preparation of which is described above (Scheme **2**) is reacted with the decahydroisoquinoline amine **19.1**, in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor thereto, such as [OH], [SH] Br, as described below, to afford the aminoalcohol product **19.2**. The conditions for the ring-opening reaction are the same as those described above for the preparation of the aminoalcohol **1.3**. The preparation of the decahydroisoquinoline derivatives **19.1** is described below, (Schemes **48a** - **52**). The cbz protecting group is then removed to yield the free amine **19.3**, using the same conditions as described above for the preparation of the amine **1.4**,

(Scheme **1**). The amine **19.3** is then coupled with the carboxylic acid or activated derivative thereof, **9.6**, using the same conditions as described above, to afford the amide **19.4**.

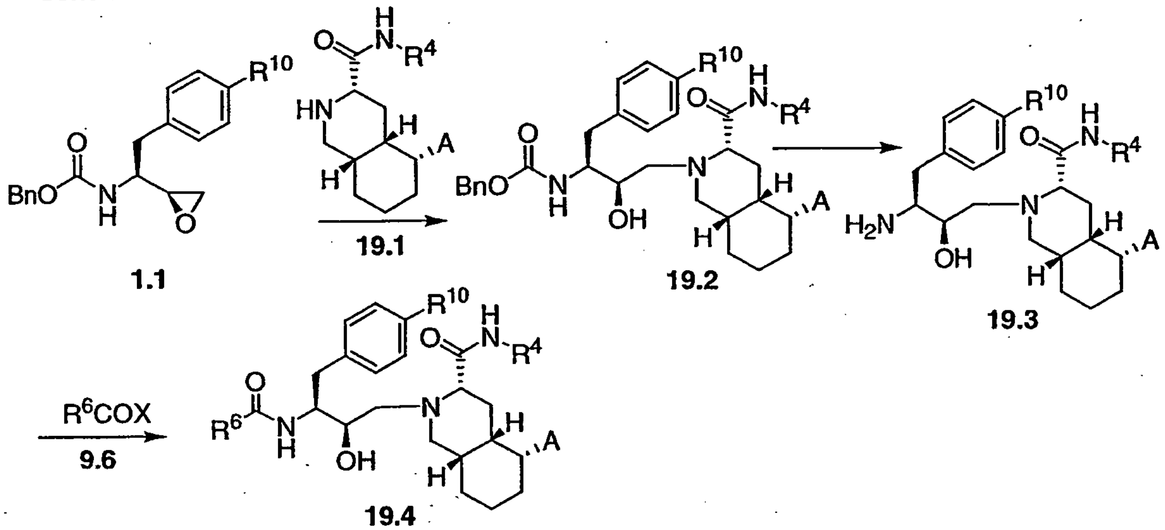
Scheme **20** illustrates an alternative method for the preparation of the phosphonate intermediates **19.4**. In this procedure, the 4-nitrobenzenesulfonyl ester **4.2**, the preparation of which is described above, (Scheme **4**) is reacted with the decahydroisoquinoline derivative **20.1**, in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. The reaction conditions for the displacement reaction are the same as those described above for the preparation of the amine **4.3**, (Scheme **4**). The oxazolidinone moiety present in the product **20.2** is then hydrolyzed, using the procedures described above (Scheme **4**) to afford the free amine **20.3**. This compound is then coupled with the carboxylic acid or activated derivative thereof, **9.6**, using the same conditions as are described above, to afford the amide product **19.4**.

The procedures illustrated in Schemes **19** and **20** depict the preparation of the compounds **19.4** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme **21** illustrates the conversion of compounds **19.4** in which A is a precursor to the group link-$P(O)(OR^1)_2$ into the compounds **4**. Procedures for the conversion of the substituent A into the group link-$P(O)(OR^1)_2$ are illustrated below, (Schemes **24** - **69**).

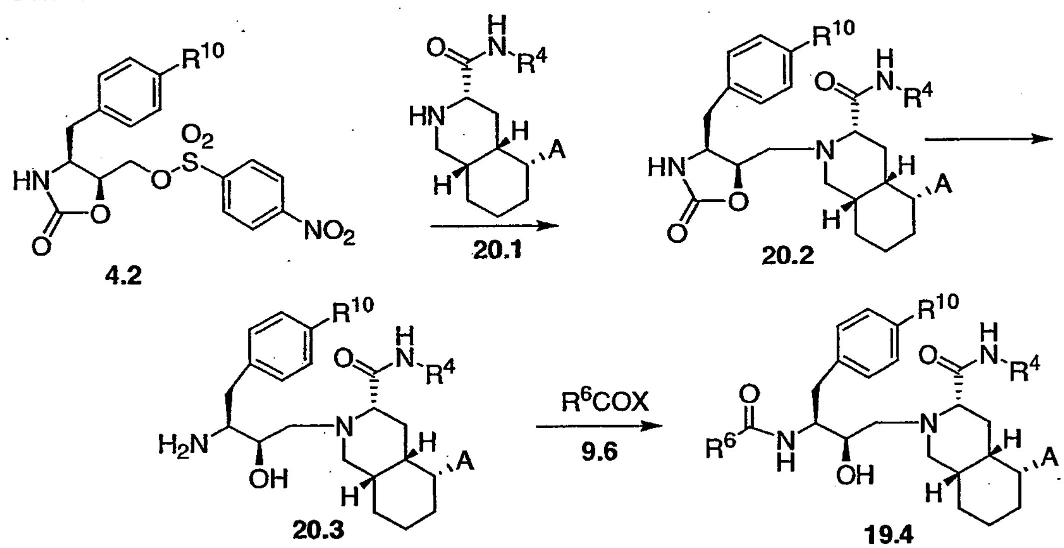
Schemes **22** and **23** depict the preparation of the phosphonate esters **4** in which X is sulfur. As shown in Scheme **22**, the oxirane **7.7**, prepared as described above (Scheme **7**) is reacted with the decahydroisoquinoline derivative **19.1**, in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. The reaction is conducted under the same conditions as described above for the preparation of the amine **7.8**, (Scheme **7**), to produce the hydroxyamine **22.1**. The cbz protecting group present in the product **22.1** is then removed, using the same procedures as described above (Scheme **7**) to afford the free amine **22.2**. This material is then coupled with the carboxylic acid or activated derivative thereof, **9.6** to yield the amide **22.3**. The coupling reaction is preformed under the same conditions as previously described.

The procedures illustrated in Scheme 22 depict the preparation of the compounds **22.3** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 23 illustrates the conversion of compounds **22.3** in which A is a precursor to the group link-P(O)(OR^1)$_2$ into the compounds **4**. Procedures for the conversion of the substituent A into the group link-P(O)(OR^1)$_2$ are illustrated below, (Schemes **24** - **69**).

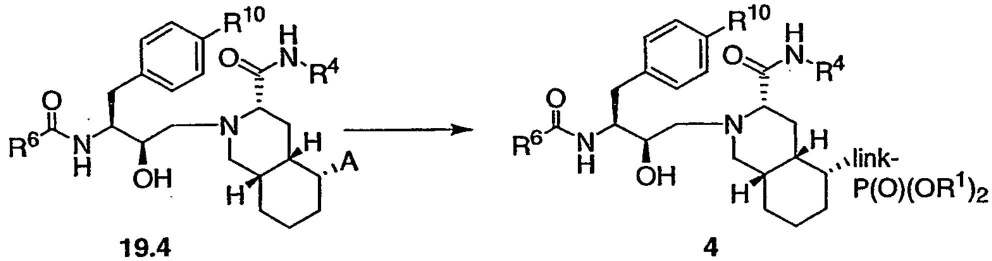
Scheme 19



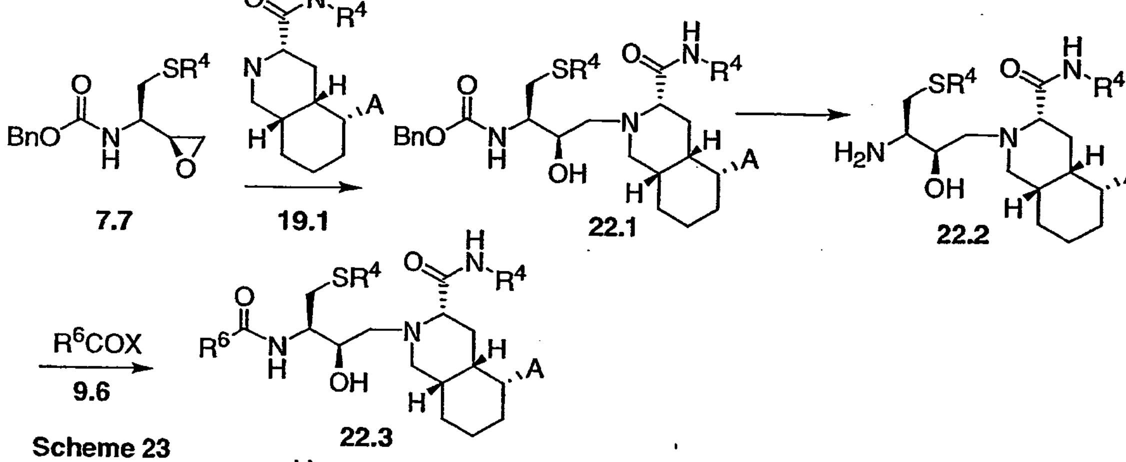
Scheme 20



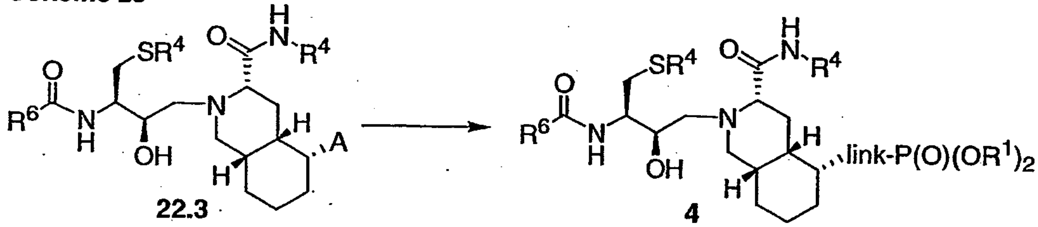
Scheme 21



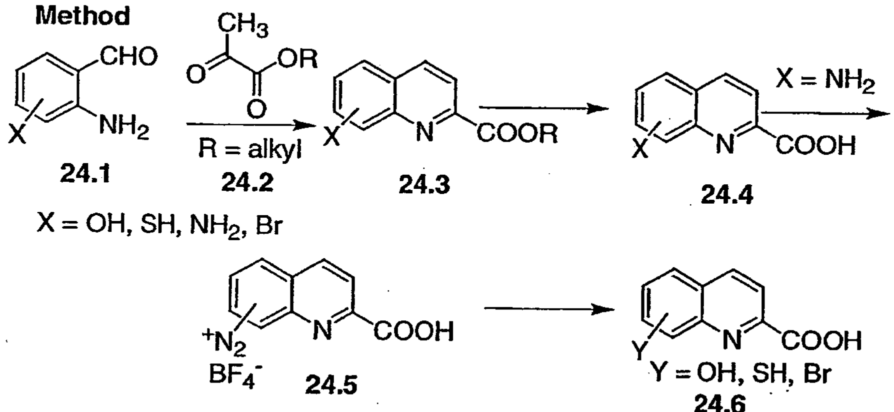
Scheme 22



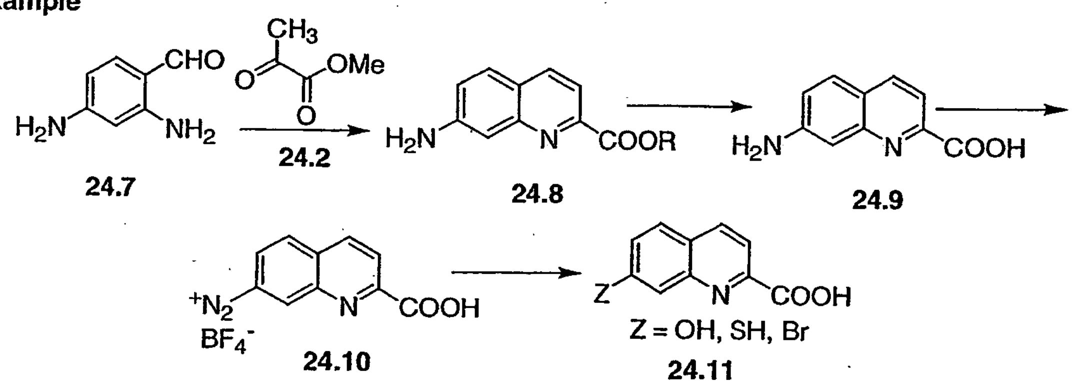
Scheme 23



Scheme 24
Method



Example



Preparation of quinoline 2-carboxylic acids 1.7 incorporating phosphonate moieties or precursors thereto.

The reaction sequence depicted in Scheme **1** requires the use of a quinoline-2-carboxylic acid reactant **1.7** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br.
A number of suitably substituted quinoline-2-carboxylic acids are available commercially or are described in the chemical literature. For example, the preparations of 6-hydroxy, 6-amino and 6-bromoquinoline-2-carboxylic acids are described respectively in DE 3004370, J. Het. Chem., 1989, 26, 929 and J. Labelled Comp. Radiopharm., 1998, 41, 1103, and the preparation of 7-aminoquinoline-2-carboxylic acid is described in J. Am. Chem. Soc., 1987, 109, 620. Suitably substituted quinoline-2-carboxylic acids can also be prepared by procedures known to those skilled in the art. The synthesis of variously substituted quinolines is described, for example, in Chemistry of Heterocyclic Compounds, Vol. 32, G. Jones, ed., Wiley, 1977, p. 93ff. Quinoline-2-carboxylic acids can be prepared by means of the Friedlander reaction, which is described in Chemistry of Heterocyclic Compounds, Vol. 4, R. C. Elderfield, ed., Wiley, 1952, p. 204.

Scheme **24** illustrates the preparation of quinoline-2-carboxylic acids by means of the Friedlander reaction, and further transformations of the products obtained. In this reaction sequence, a substituted 2-aminobenzaldehyde **24.1** is reacted with an alkyl pyruvate ester **24.2**, in the presence of an organic or inorganic base, to afford the substituted quinoline-2-carboxylic ester **24.3**. Hydrolysis of the ester, for example by the use of aqueous base, then afford the corresponding carboxylic acid **24.4**. The carboxylic acid product **24.4** in which X is NH_2 can be further transformed into the corresponding compounds **24.6** in which Z is OH, SH or Br. The latter transformations are effected by means of a diazotization reaction. The conversion of aromatic amines into the corresponding phenols and bromides by means of a diazotization reaction is described respectively in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, pages 167 and 94; the conversion of amines into the corresponding thiols is described in Sulfur Lett., 2000, 24, 123. The amine is first converted into the diazonium salt by reaction with nitrous acid. The diazonium salt, preferably the diazonium

tetrafluoborate, is then heated in aqueous solution, for example as described in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 83, to afford the corresponding phenol **24.6**, X = OH. Alternatively, the diazonium salt is reacted in aqueous solution with cuprous bromide and lithium bromide, as described in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 138, to yield the corresponding bromo compound, **24.6**, Y = Br. Alternatively, the diazonium tetrafluoborate is reacted in acetonitrile solution with a sulfhydryl ion exchange resin, as described in Sulfur Lett., 200, 24, 123, to afford the thiol **24.6**, Y = SH. Optionally, the diazotization reactions described above can be performed on the carboxylic esters **24.3** instead of the carboxylic acids **24.5**.

For example, 2,4-diaminobenzaldehyde **24.7** (Apin Chemicals) is reacted with one molar equivalent of methyl pyruvate **24.2** in methanol, in the presence if a base such as piperidine, to afford methyl-7-aminoquinoline-2-carboxylate **24.8**. Basic hydrolysis of the product, employing one molar equivalent of lithium hydroxide in aqueous methanol, then yields the carboxylic acid **24.9**. The amino-substituted carboxylic acid is then converted into the diazonium tetrafluoborate **24.10** by reaction with sodium nitrite and tetrafluoboric acid. The diazonium salt is heated in aqueous solution to afford the 7-hydroxyquinoline-2-carboxylic acid, **24.11**, Z = OH. Alternatively, the diazonium tetrafluoborate is heated in aqueous organic solution with one molar equivalent of cuprous bromide and lithium bromide, to afford 7-bromoquinoline-2-carboxylic acid **24.11**, X = Br. Alternatively, the diazonium tetrafluoborate **24.10** is reacted in acetonitrile solution with the sulfhydryl form of an ion exchange resin, as described in Sulfur Lett., 2000, 24, 123, to prepare 7-mercaptoquinoline-2-carboxylic acid **24.11**, Z = SH.

Using the above procedures, but employing, in place of 2,4-diaminobenzaldehyde **24.7**, different aminobenzaldehydes **24.1**, the corresponding amino, hydroxy, bromo or mercapto-substituted quinoline-2-carboxylic acids **24.6** are obtained. The variously substituted quinoline carboxylic acids and esters can then be transformed, as described below, (Schemes **25** – **27**) into phosphonate-containing derivatives.

Scheme **25** depicts the preparation of quinoline-2-carboxylic acids incorporating a phosphonate moiety attached to the quinoline ring by means of an oxygen or a sulfur atom. In this procedure, an amino-substituted quinoline-2-carboxylate ester **25.1** is transformed, via a

diazotization procedure as described above (Scheme **24**) into the corresponding phenol or thiol **25.2**. The latter compound is then reacted with a dialkyl hydroxymethylphosphonate **25.3**, under the conditions of the Mitsonobu reaction, to afford the phosphonate ester **25.4**. The preparation of aromatic ethers by means of the Mitsonobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4. The phenol or thiophenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the thioether products **25.5**. Basic hydrolysis of the ester group, for example employing one molar equivalent of lithium hydroxide in aqueous methanol, then yields the carboxylic acid **25.6**.

For example, methyl 6-amino-2-quinoline carboxylate **25.7**, prepared as described in J. Het. Chem., 1989, 26, 929, is converted, by means of the diazotization procedure described above, into methyl 6-mercaptoquinoline-2-carboxylate **25.8**. This material is reacted with a dialkyl hydroxymethylphosphonate **25.9** (Aldrich) in the presence of diethyl azodicarboxylate and triphenylphosphine in tetrahydrofuran solution, to afford the thioether **25.10**. Basic hydrolysis then afford the carboxylic acid **25.11**.

Using the above procedures, but employing, in place of methyl 6-amino-2-quinoline carboxylate **25.7**, different aminoquinoline carboxylic esters **25.1**, and/or different dialkyl hydroxymethylphosphonates **25.9** the corresponding phosphnoate ester products **25.3** are obtained.

Scheme **26** illustrates the preparation of quinoline-2-carboxylic acids incorporating phosphonate esters attached to the quinoline ring by means of a saturated or unsaturated carbon chain. In this reaction sequence, a bromo-substituted quinoline carboxylic ester **26.1** is coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenylphosphonate **26.2**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate.

Thus, Heck coupling of the bromo compound **26.1** and the olefin **26.2** affords the olefinic ester **26.3**. Hydrolysis, for example by reaction with lithium hydroxide in aqueous methanol, or by treatment with porcine liver esterase, then yields the carboxylic acid **26.4**. Optionally, the unsaturated carboxylic acid **26.4** can be reduced to afford the saturated analog **26.5**. The reduction reaction can be effected chemically, for example by the use of diimide or diborane, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 5. For example, methyl 7-bromoquinoline-2-carboxylate, **26.6**, prepared as described in J. Labelled Comp. Radiopharm., 1998, 41, 1103, is reacted in dimethylformamide at 60°C with a dialkyl vinylphosphonate **26.7** (Aldrich) in the presence of 2 mol% of tetrakis(triphenylphosphine)palladium and triethylamine, to afford the coupled product **26.8**. The product is then reacted with lithium hydroxide in aqueous tetrahydrofuran to produce the carboxylic acid **26.9**. The latter compound is reacted with diimide, prepared by basic hydrolysis of diethyl azodicarboxylate, as described in Angew. Chem. Int. Ed., 4, 271, 1965, to yield the saturated product **26.10**.

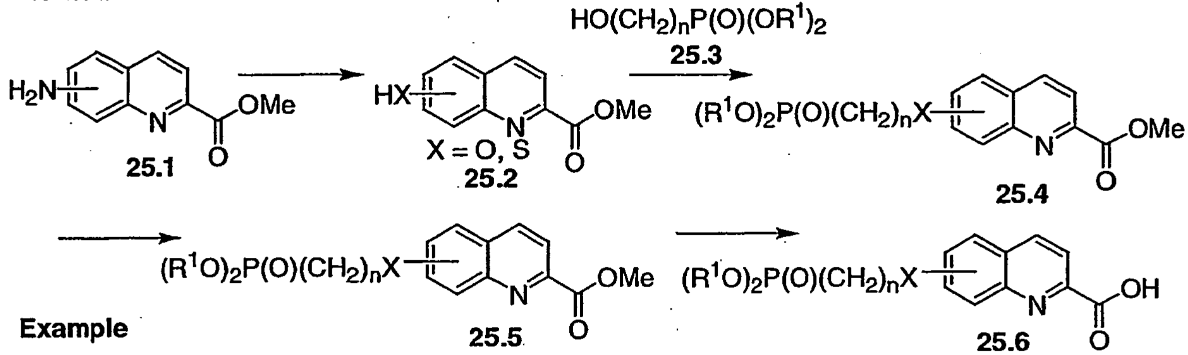
Using the above procedures, but employing, in place of methyl 6-bromo-2-quinolinecarboxylate **26.6**, different bromoquinoline carboxylic esters **26.1**, and/or different dialkyl alkenylphosphonates **26.2**, the corresponding phosphonate ester products **26.4** and **26.5** are obtained.

Scheme **27** depicts the preparation of quinoline-2-carboxylic acids **27.5** in which the phosphonate group is attached by means of a nitrogen atom and an alkylene chain. In this reaction sequence, a methyl aminoquinoline-2-carboxylate **27.1** is reacted with a phosphonate aldehyde **27.2** under reductive amination conditions, to afford the aminoalkyl product **27.3**. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in J. Org. Chem., 55, 2552, 1990. The ester product **27.4** is then hydrolyzed to yield the free carboxylic acid **27.5**.

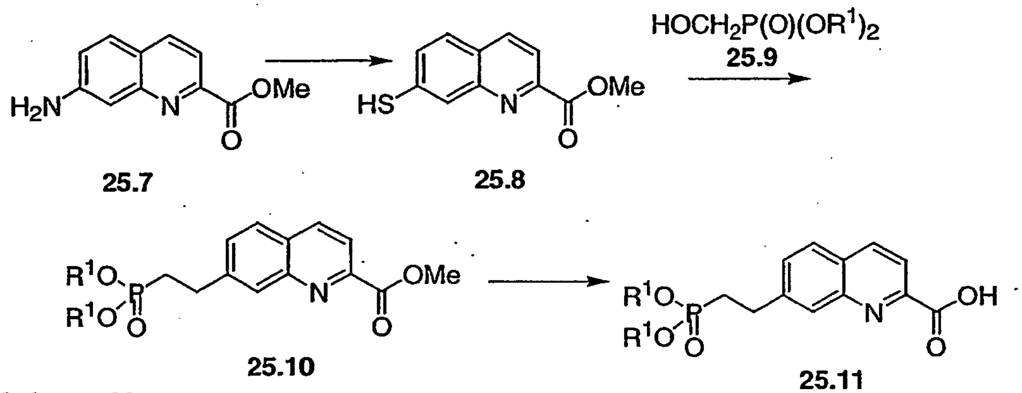
For example, methyl 7-aminoquinoline-2-carboxylate **27.6**, prepared as described in J. Amer. Chem. Soc., 1987, 109, 620, is reacted with a dialkyl formylmethylphosphonate **27.7** (Aurora) in methanol solution in the presence of sodium borohydride, to afford the alkylated product **27.8**. The ester is then hydrolyzed, as described above, to yield the carboxylic acid **27.9**. Using the above procedures, but employing, in place of the formylmethyl phosphonate **27.2**, different formylalkyl phosphonates, and/or different aminoquinolines **27.1**, the corresponding products **27.5** are obtained.

Scheme 25

Method

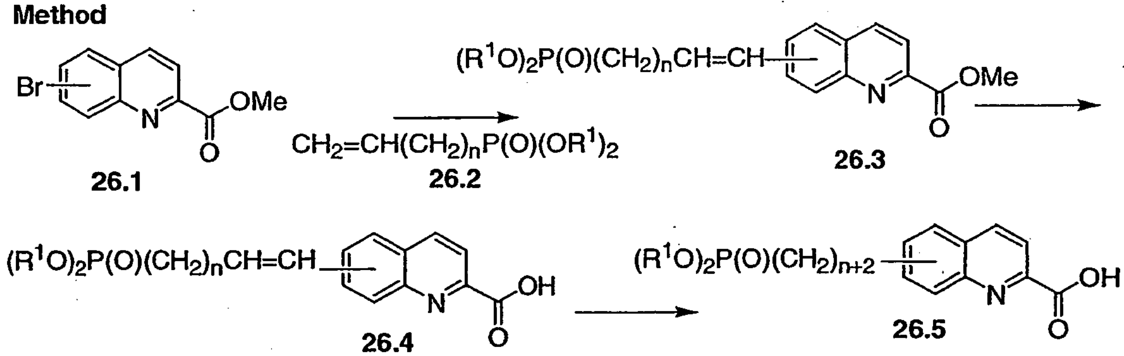


Example

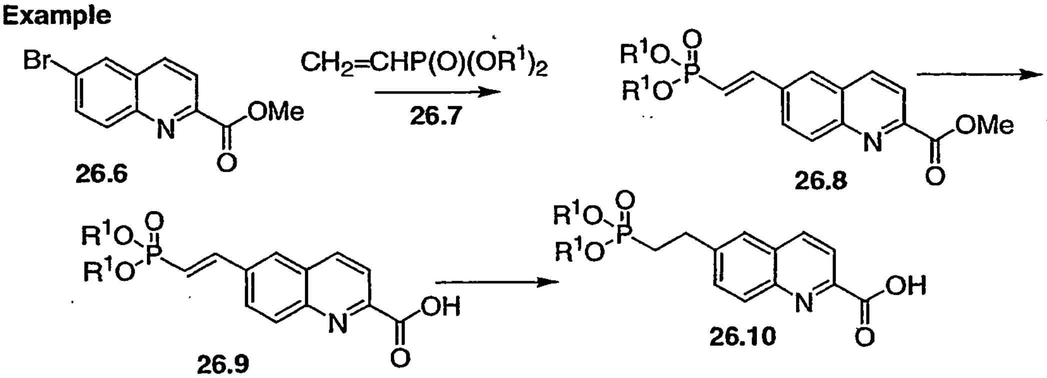


Scheme 26

Method

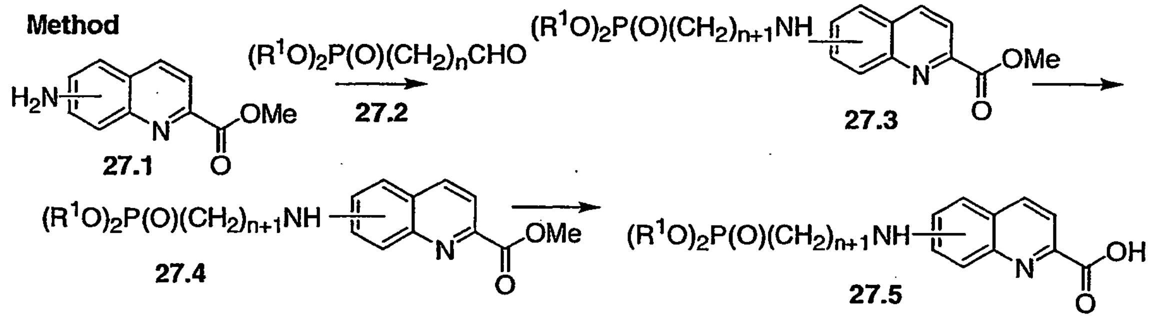


Example

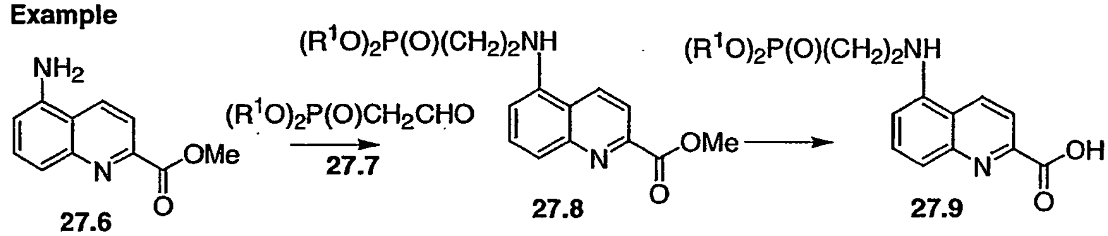


Scheme 27

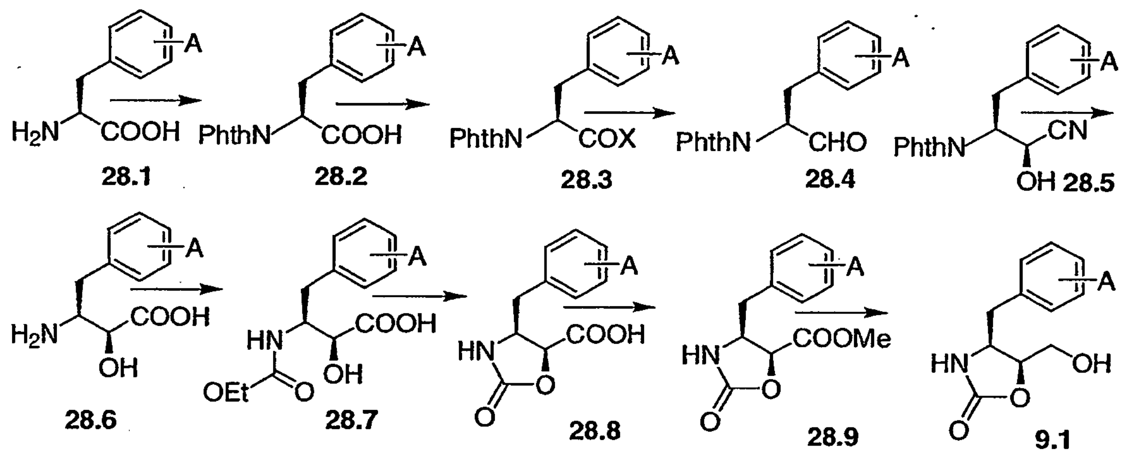
Method



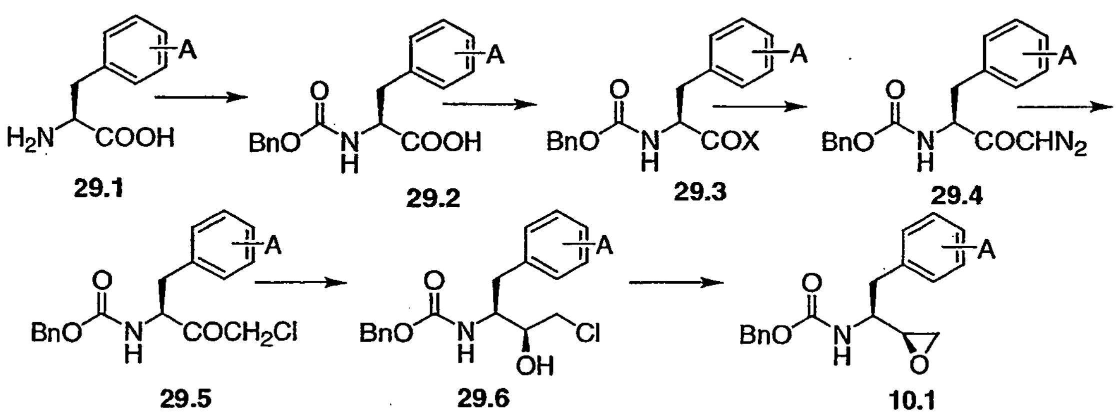
Example



Scheme 28



Scheme 29



Preparation of phenylalanine derivatives 9.1 and 10.1 incorporating phosphonate moieties or precursors thereto.

Scheme **28** illustrates the preparation of the hydroxymethyl oxazolidine derivative **9.1**, in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor thereto, such as [OH], [SH] Br. In this reaction sequence, the substituted phenylalanine **28.1**, in which A is as defined above, is transformed, via the intermediates **28.2-28.9**, into the hydroxymethyl product **9.1**. The reaction conditions for each step in the sequence are the same as those described above for the corresponding step shown in Scheme **5**. The conversion of the substituent A into the group link-P(O)(OR^1)$_2$ may be effected at any convenient step in the reaction sequence, or after the reactant **9.1** has been incorporated into the intermediates **9.5** (Scheme **9**). Specific examples of the preparation of the hydroxymethyl oxazolidinone reactant **9.1** are shown below, (Schemes **30-31**).

Scheme **29** illustrates the preparation of the oxirane intermediate **10.1**, in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor thereto, such as [OH], [SH] Br. In this reaction sequence, the substituted phenylalanine **29.1**, in which A is as defined above, is transformed, via the intermediates **29.2-29.6**, into the oxirane **10.1**. The reaction conditions for each step in the sequence are the same as those described above for the corresponding step shown in Scheme **2**. The conversion of the substituent A into the group link-P(O)(OR^1)$_2$ may be effected at any convenient step in the reaction sequence, or after the reactant **10.1** has been incorporated into the intermediates **9.5** (Scheme **10**). Specific examples of the preparation of the oxiranes reactant **10.1** are shown below, (Schemes **32-34**).

Scheme **30** depicts the preparation of hydroxymethyloxazolidinones **30.9** in which the phosphonate ester moiety is attached directly to the phenyl ring. In this procedure, a bromo-substituted phenylalanine **30.1** is converted, using the series of reactions illustrated in Scheme **28**, into the bromophenyloxazolidinone **30.2**. The bromophenyl compound is then coupled, in the presence of a palladium (0) catalyst, with a dialkyl phosphite **30.3**, to afford the phosphonate product **30.4**. The reaction between aryl bromide and dialkyl phosphites to yield aryl phosphonates is described in Synthesis, 56, 1981, and in J. Med. Chem., 1992, 35, 1371.

The reaction is conducted in an inert solvent such as toluene or xylene, at about 100°C, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium and a tertiary organic base such as triethylamine. The carbomethoxy substituent in the resultant phosphonate ester **30.4** is then reduced with sodium borohydride to the corresponding hydroxymethyl derivative **30.5**, using the procedure described above (Scheme **28**)
For example, 3-bromophenylalanine **30.6**, prepared as described in Pept. Res., 1990, 3, 176, is converted, using the sequence of reactions shown in Scheme **28**, into 4-(3-bromo-benzyl)-2-oxo-oxazolidine-5-carboxylic acid methyl ester **30.7**. This compound is then coupled with a dialkyl phosphite **30.3**, in toluene solution at reflux, in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) and triethylamine, to afford the phosphonate ester **30.8**. The carbomethoxy substituent is then reduced with sodium borohydride, as described above, to afford the hydroxymethyl product **30.9**.
Using the above procedures, but employing, in place of 3-bromophenylalanine **30.6** different bromophenylalanines **30.1** and/or different dialkyl phosphites **30.3**, the corresponding products **30.5** are obtained.

Scheme **31** illustrates the preparation of phosphonate-containing hydroxymethyl oxazolidinones **31.9** and **31.12** in which the phosphonate group is attached by means of a heteroatom and a carbon chain. In this sequence of reactions, a hydroxy or thio-substituted phenylalanine **31.1** is converted into the benzyl ester **31.2** by means of a conventional acid catalyzed esterification reaction. The hydroxyl or mercapto group is then protected. The protection of phenyl hydroxyl and thiol groups are described, respectively, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, and p. 277. For example, hydroxyl and thiol substituents can be protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the phenol or thiophenol with a chlorotrialkylsilane and a base such as imidazole, for example as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 68-86. Alternatively, thiol substituents can be protected by conversion to tert-butyl or adamantyl thioethers, or 4-methoxybenzyl thioethers, prepared by the reaction between the thiol and 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in Bull. Chem. Soc. Jpn., 37, 433, 1974. The protected ester **31.3** is then reacted with phthalic anhydride, as described above (Scheme **28**) to afford the phthalimide **31.4**. The

benzyl ester is then removed, for example by catalytic hydrogenation or by treatment with aqueous base, to afford the carboxylic acid **31.5**. This compound is transformed, by means of the series of reactions shown in Scheme **28**, into the carbomethoxy oxazolidinone **31.6**, using in each step the same conditions as are described above (Scheme **28**). The protected OH or SH group is then deprotected. Deprotection of phenols and thiophenols is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. For example, trialkylsilyl ethers or thioethers can be deprotected by treatment with a tetraalkylammonium fluoride in an inert solvent such as tetrahydrofuran, as described in J. Am Chem. Soc., 94, 6190, 1972. Tert-butyl or adamantyl thioethers can be converted into the corresponding thiols by treatment with mercuric trifluoroacetate in aqueous acetic acid at ambient temperatures, as described in Chem. Pharm. Bull., 26, 1576, 1978. The resultant phenol or thiol **31.7** is then reacted with a hydroxyalkyl phosphonate **31.20** under the conditions of the Mitsonobu reaction, as described above (Scheme **25**), to afford the ether or thioether **31.8**. The latter compound is then reduced with sodium borohydride, as described above (Scheme **28**) to afford the hydroxymethyl analog **31.9**.

Alternatively, the phenol or thiophenol **31.7** is reacted with a dialkyl bromoalkyl phosphonate **31.10** to afford the alkylation product **31.11**. The alkylation reaction is preformed in a polar organic solvent such as dimethylformamide, acetonitrile and the like, optionally in the presence of potassium iodide, and in the presence of an inorganic base such as potassium or cesium carbonate, or an organic base such as diazabicyclononene or dimethylaminopyridine. The ether or thioether product is then reduced with sodium borohydride to afford the hydroxymethyl compound **31.12**.

For example, 3-hydroxyphenylalanine **31.13** (Fluka) is converted in to the benzyl ester **31.14** by means of a conventional acid-catalyzed esterification reaction. The ester is then reacted with tert-butylchlorodimethylsilane and imidazole in dimethylformamide, to afford the silyl ether **31.15**. The protected ether is then reacted with phthalic anhydride, as described above (Scheme **28**) to yield the phthalimido-protected compound **31.16**. Basic hydrolysis, for example by reaction with lithium hydroxide in aqueous methanol, then affords the carboxylic acid **31.17**. This compound is then transformed, by means of the series of reactions shown in Scheme **28**, into the carbomethoxy-substituted oxazolidinone **31.18**. The silyl protecting group is then removed by treatment with tetrabutylammonium fluoride in tetrahydrofuran at ambient temperature, to produce the phenol **31.19**. The latter compound is reacted with a

dialkyl hydroxymethyl phosphonate **31.20** diethylazodicarboxylate and triphenylphosphine, by means of the Mitsonobu reaction, as described above (Scheme **25**) to yield the phenolic ether **31.21**. The carbomethoxy group is then reduced by reaction with sodium borohydride, as described above, to afford the carbinol **31.22**.

Using the above procedures, but employing, in place of 3-hydroxyphenylalanine **31.13**, different hydroxy or mercapto-substituted phenylalanines **31.1**, and/or different dialkyl hydroxyalkyl phosphonates **31.20**, the corresponding products **31.9** are obtained.

As a further example of the methods illustrated in Scheme **31**, 4-mercaptophenylalanine **31.23**, prepared as described in J. Amer. Chem. Soc., 1997, 119, 7173, is converted into the benzyl ester **31.24** by means of a conventional acid-catalyzed esterification reaction. The mercapto group is then protected by conversion to the S-adamantyl group, by reaction with 1-adamantanol and trifluoroacetic acid at ambient temperature as described in Chem. Pharm. Bull., 26, 1576, 1978. The amino group is then converted into the phthalimido group as described above, and the ester moiety is hydrolyzed with aqueous base to afford the carboxylic acid **31.27**. The latter compound is then transformed, by means of the series of reactions shown in Scheme **28**, into the carbomethoxy oxazolidinone **31.28**. The adamantyl protecting group is then removed by treatment of the thioether **31.28** with mercuric acetate in trifluoroacetic acid at 0°C, as described in Chem. Pharm. Bull., 26, 1576, 1978, to produce the thiol **31.29**. The thiol is then reacted with one molar equivalent of a dialkyl bromoethylphosphonate **31.30**, (Aldrich) and cesium carbonate in dimethylformamide at 70°C, to afford the thioether product **31.31**. The carbomethoxy group is then reduced with sodium borohydride, as described above, to prepare the carbinol **31.32**.

Using the above procedures, but employing, in place of 4-mercaptophenylalanine **31.23**, different hydroxy or mercapto-substituted phenylalanines **31.10**, and/or different dialkyl bromoalkyl phosphonates **31.10**, the corresponding products **31.12** are obtained.

Scheme **32** illustrates the preparation of phenylalanine derivatives **32.3** in which the phosphonate group is attached directly to the phenyl ring. In this procedure, a bromo-substituted phenylalanine **32.1** is converted, by means of the series of reactions shown in Scheme **29** into the oxirane **32.2**. This compound is then coupled with a dialkyl phosphite **30.3**, in the presence of a palladium(0) catalyst and an organic base, to afford the phosphonate

oxirane **32.3**. The coupling reaction is performed under the same conditions previously described, (Scheme **30**).

For example, 3-bromophenylalanine **32.4**, prepared as described in Pept. Res., 1990, 3, 176, is converted, as described above, into the oxirane **32.5**. This compound is reacted, in toluene solution at reflux temperature, with a dialkyl phosphonate **30.3**, in the presence of tetrakis(triphenylphosphine)palladium(0) and triethylamine to afford the phosphonate ester **32.6**.

Using the above procedures, but employing, in place of 4-bromophenylalanine **32.4**, different bromo-substituted phenylalanines **32.1**, and/or different dialkyl phosphites **30.3**, the corresponding products **32.3** are obtained.

Scheme **33** depicts the preparation of compounds **33.4** in which the phosphonate group is attached to the phenyl ring by means of a styrene moiety. In this reaction sequence, a vinyl-substituted phenylalanine **33.1** is converted, by means of the series of reactions shown in Scheme **29**, into the oxirane **33.2**. This compound is then coupled with a dialkyl bromophenylphosphonate **33.3**, employing the conditions of the Heck reaction, as described above (Scheme **26**) to afford the coupled product **33.4**.

For example, 4-vinylphenylalanine **33.5**, prepared as described in EP 206460, is converted, as described above, into the oxirane **33.6**. This compound is then coupled with a dialkyl 4-bromophenylphosphonate **33.7**, prepared as described in J. Chem. Soc. Perkin Trans., 1977, 2, 789, using tetrakis(triphenylphosphine)palladium(0) as catalyst, to yield the phosphonate ester **33.8**.

Using the above procedures, but employing, in place of 4-vinylphenylalanine **33.5**, different vinyl-substituted phenylalanines **33.1**, and/or different dialkyl bromophenylphosphonates **33.3**, the corresponding products **33.4** are obtained.

Scheme **34** depicts the preparation of phosphonate-substituted phenylalanine derivatives in which the phosphonate moiety is attached by means of an alkylene chain incorporating a heteroatom. In this procedure, a hydroxymethyl-substituted phenylalanine **34.1** is converted into the cbz protected methyl ester **34.2**, using the procedures described above (Scheme **29**). The product **34.2** is then converted into a halomethyl-substituted compound **34.3**. For example, the carbinol **34.2** is treated with triphenylphosphine and carbon tetrabromide, as

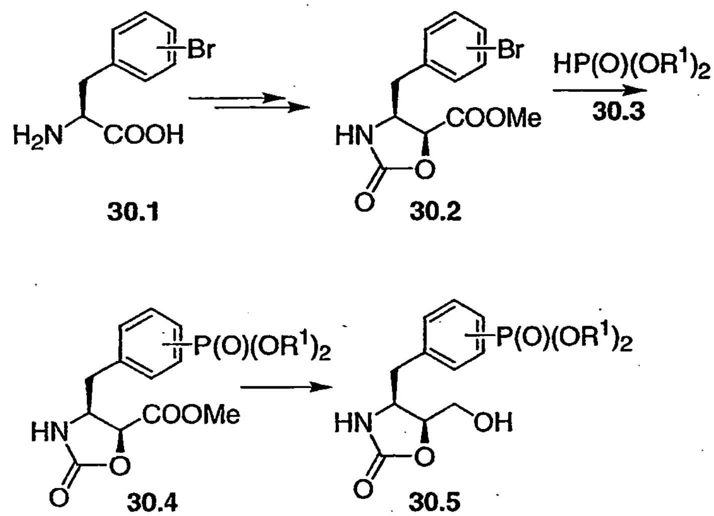
described in J. Amer. Chem. Soc., 108, 1035, 1986 to afford the product **34.3** in which Z is Br. The bromo compound is then reacted with a dialkyl terminally hetero-substituted alkylphosphonate **34.4**. The reaction is accomplished in the presence of a base, the nature of which depends on the nature of the substituent X. For example, if X is SH, NH_2 or NHalkyl, an inorganic base such as cesium carbonate, or an organic base such as diazabicyclononene or dimethylaminopyridine, can be employed. If X is OH, a strong base such as lithium hexamethyldisilylazide or the like can be employed. The condensation reaction affords the phosphonate-substituted ester **34.5**, which is hydrolyzed to afford the carboxylic acid **34.6**. The latter compound is then, by means of the sequence of reactions shown in Scheme **29**, is transformed into the epoxide **34.7**.

For example, the protected 4-hydroxymethyl-substituted phenylalanine derivative **34.9**, obtained from the 4-hydroxymethyl phenylalanine **34.8**, the preparation of which is described in Syn. Comm., 1998, 28, 4279, is converted into the bromo derivative **34.10**, as described above. The product is then reacted with a dialkyl 2-aminoethyl phosphonate **34.11**, the preparation of which is described in J. Org. Chem., 2000, 65, 676, in the presence of cesium carbonate in dimethylformamide at ambient temperature, to afford the amine product **34.12**. The latter compound is then converted, using the sequence of reactions shown in Scheme **29**, into the epoxide **34.14**.

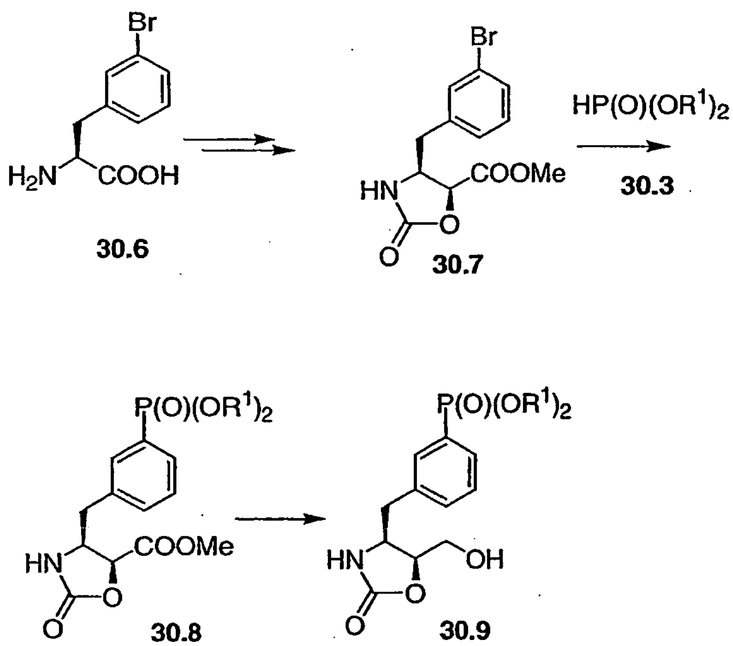
Using the above procedures, but employing different carbinols **34.1** in place of the carbinol **34.8**, and/or different phosphonates **34.4**, the corresponding products **34.7** are obtained.

Scheme 30

Method

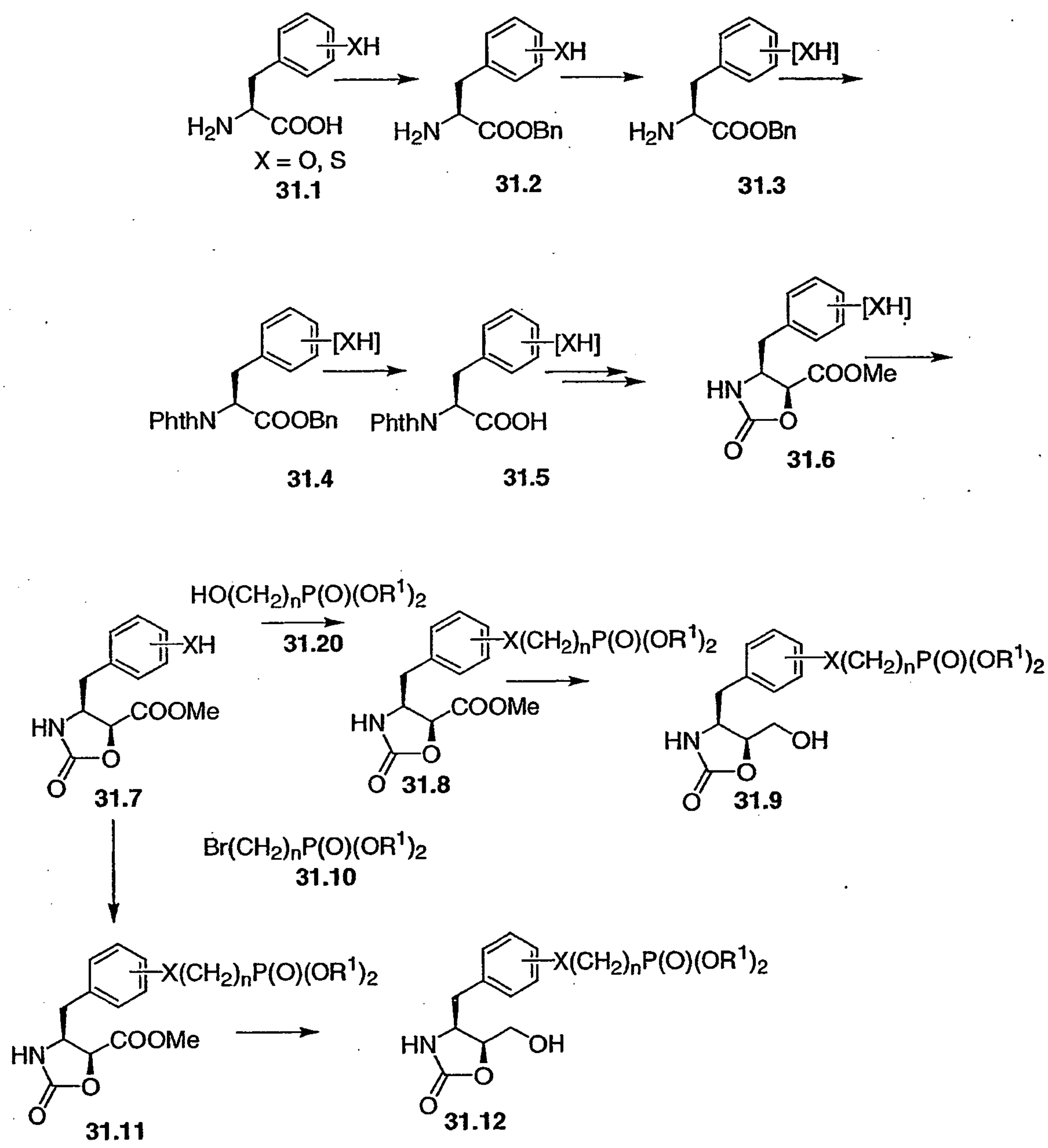


Example

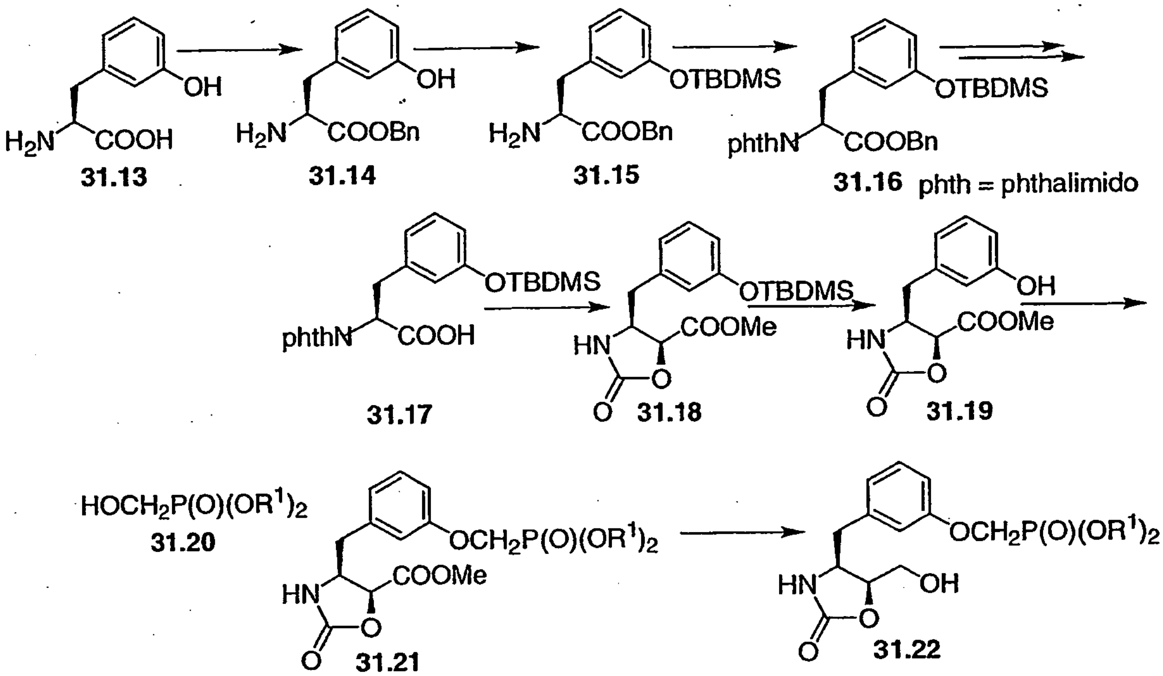


Scheme 31

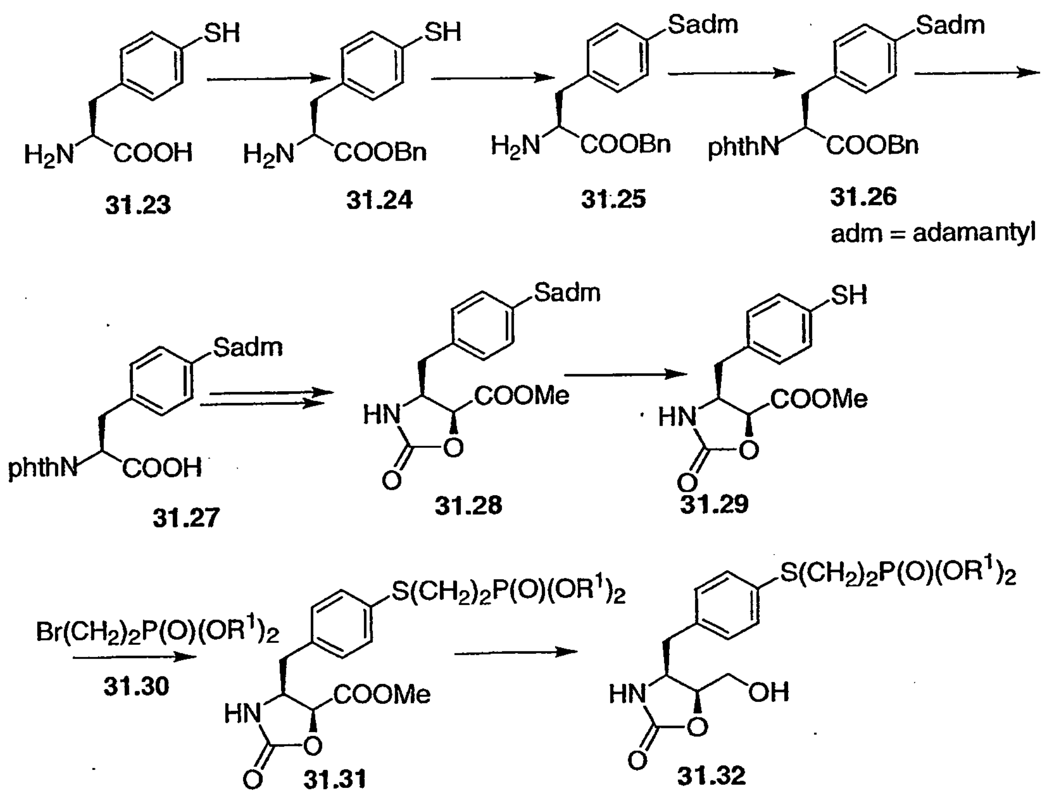
Method



Scheme 31 Example 1

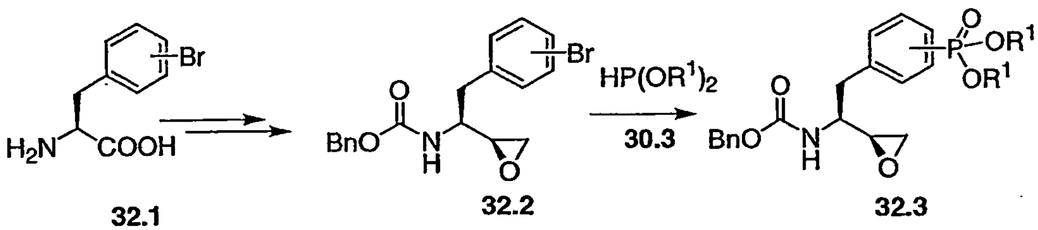


Scheme 31 Example 2

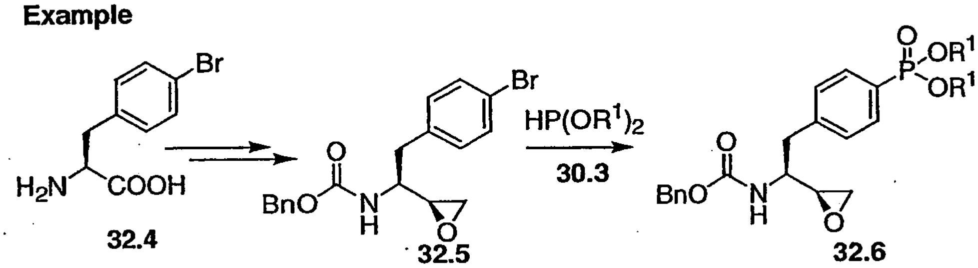


Scheme 32

Method

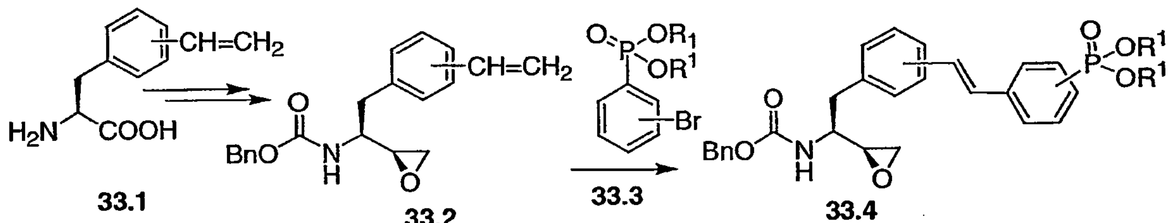


Example

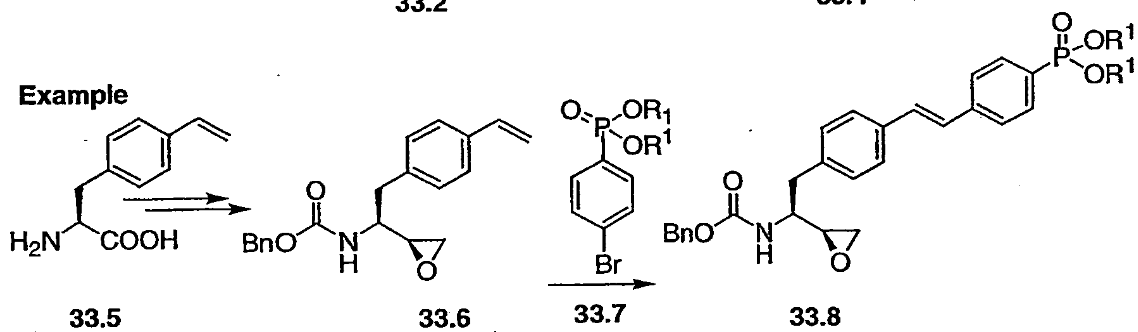


Scheme 33

Method

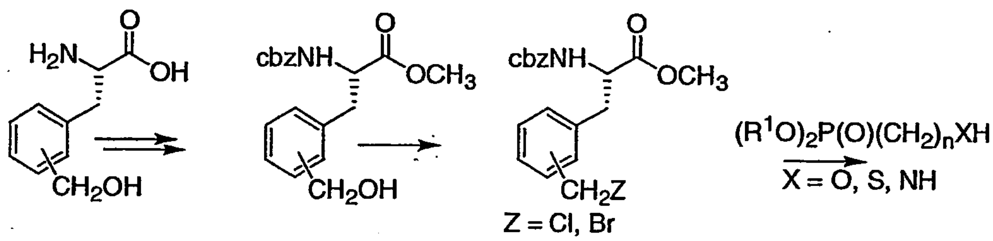


Example

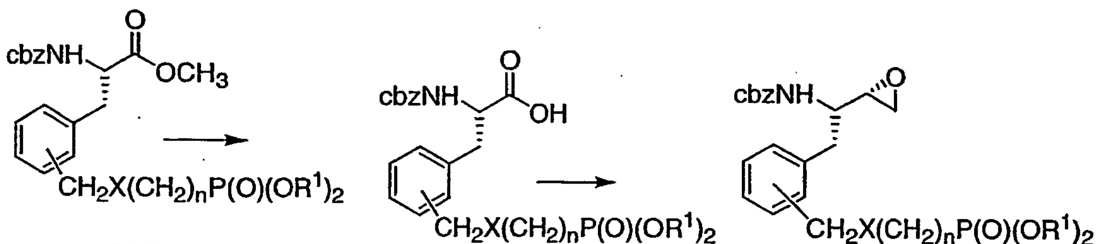


Scheme 34

Method

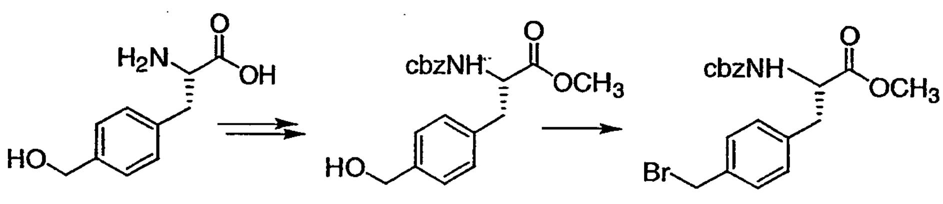


34.1 34.2 34.3 34.4

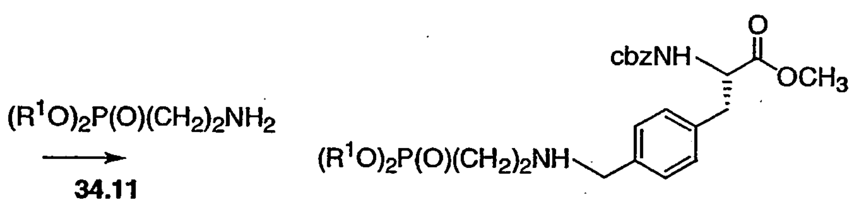


34.5 34.6 34.7

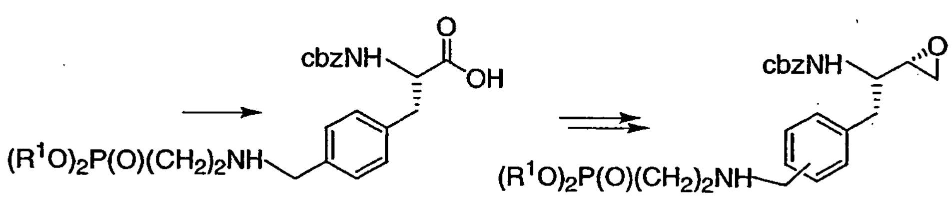
Example



34.8 34.9 34.10



34.12



34.13 34.14

Preparation of thiophenols 12.2 incorporating phosphonate groups.

Scheme **35** illustrates the preparation of thiophenols in which a phosphonate moiety is attached directly to the aromatic ring. In this procedure, a halo-substituted thiophenol **35.1** is subjected to a suitable protection procedure. The protection of thiophenols is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 277ff. The protected compound **35.2** is then coupled, under the influence of a transition metal catalyst, with a dialkyl phosphite **30.3**, to afford the product **35.3**. The product is then deprotected to afford the free thiophenol **35.4**. Suitable protecting groups for this procedure include alkyl groups such as triphenylmethyl and the like. Palladium (0) catalysts are employed, and the reaction is conducted in an inert solvent such as benzene, toluene and the like, as described in J. Med. Chem., 35, 1371, 1992. Preferably, the 3-bromothiophenol **35.5** is protected by conversion to the 9-fluorenylmethyl derivative **35.6,** as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 284, and the product is reacted in toluene with a dialkyl phosphite in the presence of tetrakis(triphenylphosphine)palladium (0) and triethylamine, to yield the product **35.7**. Deprotection, for example by treatment with aqueous ammonia in the presence of an organic co-solvent, as described in J. Chem. Soc. Chem. Comm. 1501, 1986, then gives the thiol **35.8**.

Using the above procedures, but employing, in place of the bromo compound **35.5**, different bromo compounds **35.2**, and/or different phosphonates **30.3**, there are obtained the corresponding thiols **35.4**.

Scheme **36** illustrates an alternative method for obtaining thiophenols with a directly attached phosphonate group. In this procedure, a suitably protected halo-substituted thiophenol **36.2** is metallated, for example by reaction with magnesium or by transmetallation with an alkyllithium reagent, to afford the metallated derivative **36.3**. The latter compound is reacted with a halodialkyl phosphate **36.4,** followed by deprotection as described previously, to afford the product **36.5**.

For example, 4-bromothiophenol **36.7** is converted into the S-triphenylmethyl (trityl) derivative **36.8**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 287. The product is converted into the lithium derivative **36.9**

by reaction with butyllithium in an ethereal solvent at low temperature, and the resulting lithio compound is reacted with a dialkyl chlorodiethyl phosphite **36.10** to afford the phosphonate **36.11**. Removal of the trityl group, for example by treatment with dilute hydrochloric acid in acetic acid, as described in J. Org. Chem., 31, 1118, 1966, then affords the thiol **36.12**. Using the above procedures, but employing, in place of the bromo compound **36.7**, different halo compounds **36.2**, and/or different halo dialkyl phosphites **36.4**, there are obtained the corresponding thiols **36.6**.

Scheme **37** illustrates the preparation of phosphonate-substituted thiophenols in which the phosphonate group is attached by means of a one-carbon link. In this procedure, a suitably protected methyl-substituted thiophenol **37.1** is subjected to free-radical bromination to afford a bromomethyl product **37.1a**. This compound is reacted with a sodium dialkyl phosphite **37.2** or a trialkyl phosphite, to give the displacement or rearrangement product **37.3**, which upon deprotection affords the thiophenols **37.4**.

For example, 2-methylthiophenol **37.5** is protected by conversion to the benzoyl derivative **37.6**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298. The product is reacted with N-bromosuccinimide in ethyl acetate to yield the bromomethyl product **37.7**. This material is reacted with a sodium dialkyl phosphite **37.2**, as described in J. Med. Chem., 35, 1371, 1992, to afford the product **37.8**. Alternatively, the bromomethyl compound **37.7** can be converted into the phosphonate **37.8** by means of the Arbuzov reaction, for example as described in Handb. Organophosphorus Chem., 1992, 115. In this procedure, the bromomethyl compound **37.7** is heated with a trialkyl phosphate $P(OR^1)_3$ at ca. 100^0C to produce the phosphonate **37.8**. Deprotection of **37.8**, for example by treatment with aqueous ammonia, as described in J. Amer. Chem. Soc., 85, 1337, 1963, then affords the thiol **37.9**.

Using the above procedures, but employing, in place of the bromomethyl compound **37.7**, different bromomethyl compounds **37.2**, there are obtained the corresponding thiols **37.4**.

Scheme **38** illustrates the preparation of thiophenols bearing a phosphonate group linked to the phenyl nucleus by oxygen or sulfur. In this procedure, a suitably protected hydroxy or thio-substituted thiophenol **38.1** is reacted with a dialkyl hydroxyalkylphosphonate **38.2** under the conditions of the Mitsonobu reaction, for example as described in Org. React., 1992, 42,

335, to afford the coupled product **38.3**. Deprotection then yields the O- or S-linked products **38.4**.

For example, the substrate 3-hydroxythiophenol, **38.5**, is converted into the monotrityl ether **38.6**, by reaction with one equivalent of trityl chloride, as described above. This compound is reacted with diethyl azodicarboxylate, triphenyl phosphine and a dialkyl 1-hydroxymethyl phosphonate **38.7** in benzene, as described in Synthesis, 4, 327, 1998, to afford the ether compound **38.8**. Removal of the trityl protecting group, as described above, then affords the thiophenol **38.9**.

Using the above procedures, but employing, in place of the phenol **38.5**, different phenols or thiophenols **38.1**, and /or different phosphonates **38.2**, there are obtained the corresponding thiols **38.4**.

Scheme **39** illustrates the preparation of thiophenols **39.4** bearing a phosphonate group linked to the phenyl nucleus by oxygen, sulfur or nitrogen. In this procedure, a suitably protected O, S or N-substituted thiophenol **39.1** is reacted with an activated ester, for example the trifluoromethanesulfonate **39.2**, of a dialkyl hydroxyalkyl phosphonate, to afford the coupled product **39.3**. Deprotection then affords the thiol **39.4**.

For example, 4-methylaminothiophenol **39.5**, is reacted with one equivalent of acetyl chloride, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298, to afford the product **39.6**. This material is then reacted with, for example, a dialkyl trifluoromethanesulfonylmethyl phosphonate **39.7**, the preparation of which is described in Tet. Lett., 1986, 27, 1477, to afford the displacement product **39.8**. Preferably, equimolar amounts of the phosphonate **39.7** and the amine **39.6** are reacted together in an aprotic solvent such as dichloromethane, in the presence of a base such as 2,6-lutidine, at ambient temperatures, to afford the phosphonate product **39.8**. Deprotection, for example by treatment with dilute aqueous sodium hydroxide for two minutes, as described in J. Amer. Chem. Soc., 85, 1337, 1963, then affords the thiophenol **39.9**.

Using the above procedures, but employing, in place of the thioamine **39.5**, different phenols, thiophenols or amines **39.1**, and/or different phosphonates **39.2**, there are obtained the corresponding products **39.4**.

Scheme **40** illustrates the preparation of phosphonate esters linked to a thiophenol nucleus by means of a heteroatom and a multiple-carbon chain, employing a nucleophilic displacement reaction on a dialkyl bromoalkyl phosphonate **40.2**. In this procedure, a suitably protected

hydroxy, thio or amino substituted thiophenol **40.1** is reacted with a dialkyl bromoalkyl phosphonate **40.2** to afford the product **40.3**. Deprotection then affords the free thiophenol **40.4**.

For example, 3-hydroxythiophenol **40.5** is converted into the S-trityl compound **40.6**, as described above. This compound is then reacted with, for example, a dialkyl 4-bromobutyl phosphonate **40.7**, the synthesis of which is described in Synthesis, 1994, 9, 909. The reaction is conducted in a dipolar aprotic solvent, for example dimethylformamide, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of potassium iodide, at about 50°C to yield the ether product **40.8**. Deprotection, as described above, then affords the thiol **40.9**.

Using the above procedures, but employing, in place of the phenol **40.5**, different phenols, thiophenols or amines **40.1**, and/or different phosphonates **40.2**, there are obtained the corresponding products **40.4**.

Scheme **41** depicts the preparation of phosphonate esters linked to a thiophenol nucleus by means of unsaturated and saturated carbon chains. The carbon chain linkage is formed by means of a palladium catalyzed Heck reaction, in which an olefinic phosphonate **41.2** is coupled with an aromatic bromo compound **41.1**. Deprotection, or hydrogenation of the double bond followed by deprotection, affords respectively the unsaturated phosphonate **41.4**, or the saturated analog **41.6**.

For example, 3-bromothiophenol is converted into the S-Fm derivative **41.7**, as described above, and this compound is reacted with diethyl 1-butenyl phosphonate **41.8**, the preparation of which is described in J. Med. Chem., 1996, 39, 949, in the presence of a palladium (II) catalyst, for example, bis(triphenylphosphine) palladium (II) chloride, as described in J. Med. Chem, 1992, 35, 1371. The reaction is conducted in an aprotic dipolar solvent such as, for example, dimethylformamide, in the presence of triethylamine, at about 100°C to afford the coupled product **41.9**. Deprotection, as described above, then affords the thiol **41.10**. Optionally, the initially formed unsaturated phosphonate **41.9** can be subjected to catalytic hydrogenation, using, for example, palladium on carbon as catalyst, to yield the saturated product **41.11**, which upon deprotection affords the thiol **41.12**.

Using the above procedures, but employing, in place of the bromo compound **41.7**, different bromo compounds **41.1**, and/or different phosphonates **41.2**, there are obtained the corresponding products **41.4** and **41.6**

Scheme **42** illustrates the preparation of an aryl-linked phosphonate ester **42.4** by means of a palladium(0) or palladium(II) catalyzed coupling reaction between a bromobenzene and a phenylboronic acid, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 57. The sulfur-substituted phenylboronic acid **42.1** is obtained by means of a metallation-boronation sequence applied to a protected bromo-substituted thiophenol, for example as described in J. Org. Chem., 49, 5237, 1984. A coupling reaction then affords the diaryl product **42.3** which is deprotected to yield the thiol **42.4**.
For example, protection of 4-bromothiophenol by reaction with tert-butylchlorodimethylsilane, in the presence of a base such as imidazole, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 297, followed by metallation with butyllithium and boronation, as described in J. Organomet. Chem., 1999, 581, 82, affords the boronate **42.5**. This material is reacted with diethyl 4-bromophenylphosphonate **42.6**, the preparation of which is described in J. Chem. Soc., Perkin Trans., 1977, 2, 789, in the presence of tetrakis(triphenylphosphine) palladium (0) and an inorganic base such as sodium carbonate, to afford the coupled product **42.7**. Deprotection, for example by the use of tetrabutylammonium fluoride in anhydrous tetrahydrofuran, then yields the thiol **42.8**.
Using the above procedures, but employing, in place of the boronate **42.5**, different boronates **42.1**, and/or different phosphonates **42.2**, there are obtained the corresponding products **42.4**.

Scheme **43** depicts the preparation of dialkyl phosphonates in which the phosphonate moiety is linked to the thiophenyl group by means of a chain which incorporates an aromatic or heteroaromatic ring. In this procedure, a suitably protected O, S or N-substituted thiophenol **43.1** is reacted with a dialkyl bromomethyl-substituted aryl or heteroarylphosphonate **43.2**, prepared, for example, by means of an Arbuzov reaction between equimolar amounts of a bis(bromo-methyl) substituted aromatic compound and a trialkyl phosphite. The reaction product **43.3** is then deprotected to afford the thiol **43.4**. For example, 1,4-dimercaptobenzene is converted into the monobenzoyl ester **43.5** by reaction with one molar equivalent of benzoyl chloride, in the presence of a base such as pyridine. The monoprotected thiol **43.5** is then reacted with, for example diethyl 4-(bromomethyl)phenylphosphonate, **43.6**,

the preparation of which is described in Tetrahedron, 1998, 54, 9341. The reaction is conducted in a solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, at about 50°C. The thioether product **43.7** thus obtained is deprotected, as described above, to afford the thiol **43.8**.

Using the above procedures, but employing, in place of the thiophenol **43.5**, different phenols, thiophenols or amines **43.1**, and/or different phosphonates **43.2**, there are obtained the corresponding products **43.4**.

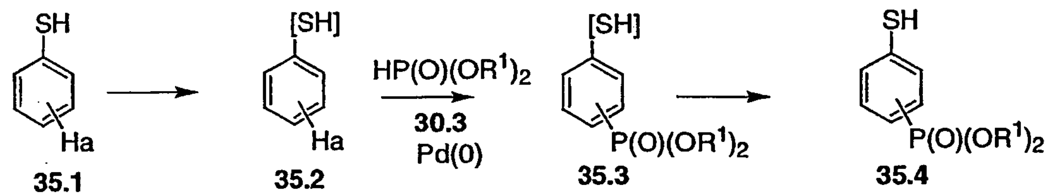
Scheme **44** illustrates the preparation of phosphonate-containing thiophenols in which the attached phosphonate chain forms a ring with the thiophenol moiety.

In this procedure, a suitably protected thiophenol **44.1**, for example an indoline (in which X-Y is $(CH_2)_2$), an indole (X-Y is CH=CH) or a tetrahydroquinoline (X-Y is $(CH_2)_3$) is reacted with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **44.2**, in the presence of an organic or inorganic base, in a polar aprotic solvent such as, for example, dimethylformamide, to afford the phosphonate ester **44.3**. Deprotection, as described above, then affords the thiol **44.4**. The preparation of thio-substituted indolines is described in EP 209751. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding hydroxy-substituted compounds, for example by thermal rearrangement of the dimethylthiocarbamoyl esters, as described in J. Org. Chem., 31, 3980, 1966. The preparation of hydroxy-substituted indoles is described in Syn., 1994, 10, 1018; preparation of hydroxy-substituted indolines is described in Tet. Lett., 1986, 27, 4565, and the preparation of hydroxy-substituted tetrahydroquinolines is described in J. Het. Chem., 1991, 28, 1517, and in J. Med. Chem., 1979, 22, 599. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding amino and bromo compounds, respectively by diazotization, as described in Sulfur Letters, 2000, 24, 123, or by reaction of the derived organolithium or magnesium derivative with sulfur, as described in Comprehensive Organic Functional Group Preparations, A. R. Katritzky et al, eds, Pergamon, 1995, Vol. 2, p 707. For example, 2,3-dihydro-1H-indole-5-thiol, **44.5**, the preparation of which is described in EP 209751, is converted into the benzoyl ester **44.6**, as described above, and the ester is then reacted with the triflate **44.7**, using the conditions described above for the preparation of **39.8**, (Scheme **39**, to yield the phosphonate **44.8**. Deprotection, for example by reaction with dilute aqueous ammonia, as described above, then affords the thiol **44.9**.

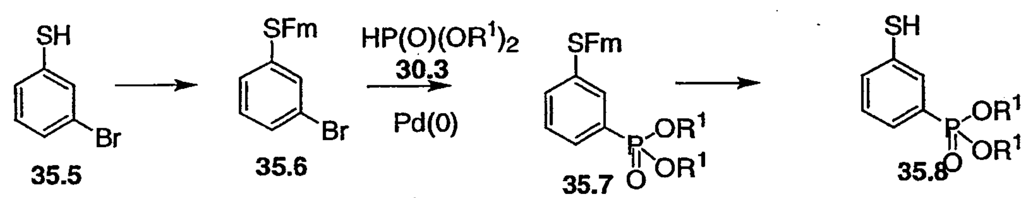
Using the above procedures, but employing, in place of the thiol **44.5**, different thiols **44.1**, and/or different triflates **44.2**, there are obtained the corresponding products **44.4**.

Scheme 35

Method



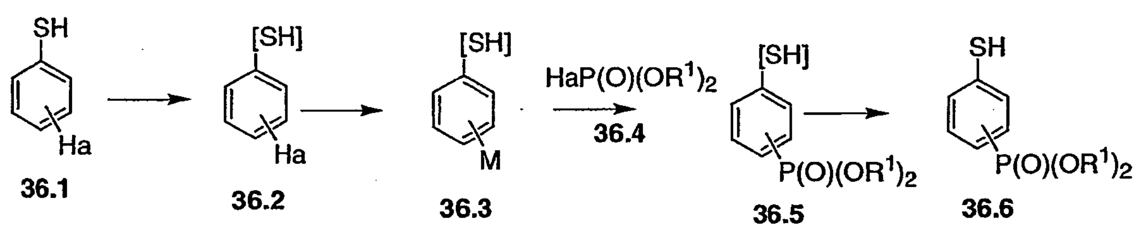
Example



Fm = 9-fluorenylmethyl

Scheme 36

Method



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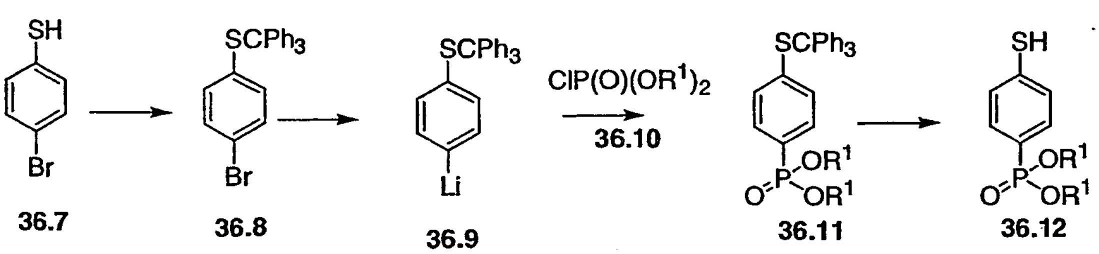
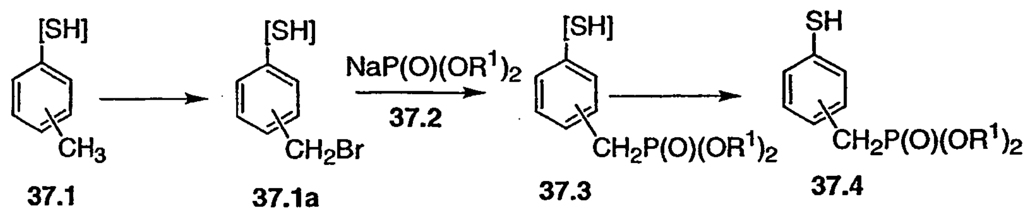


Scheme 37

Method



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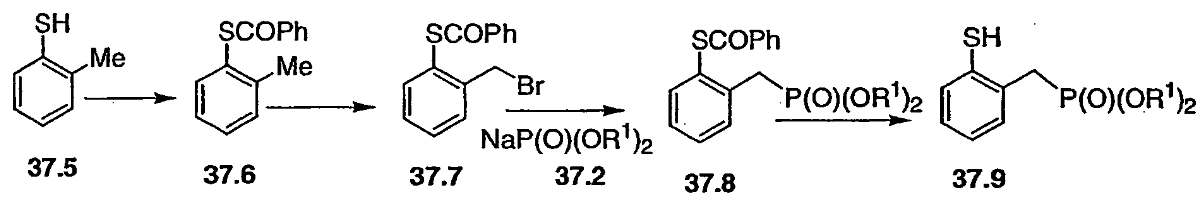
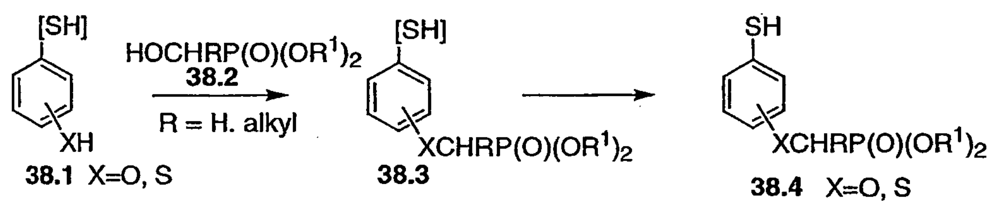


Scheme 38

Method



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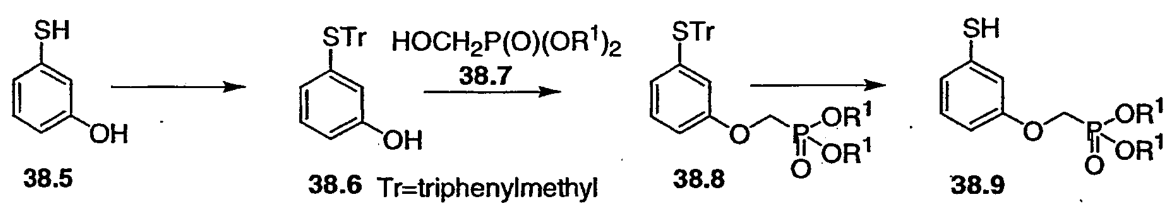
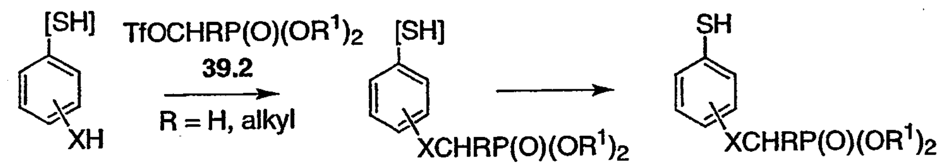


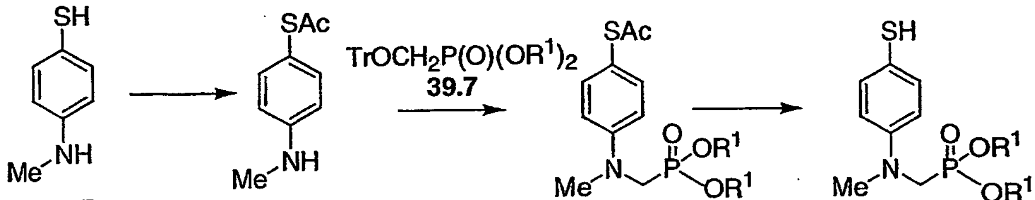
Scheme 39

Method



39.1 X=O,S, NH, Nalkyl **39.3** **39.4**

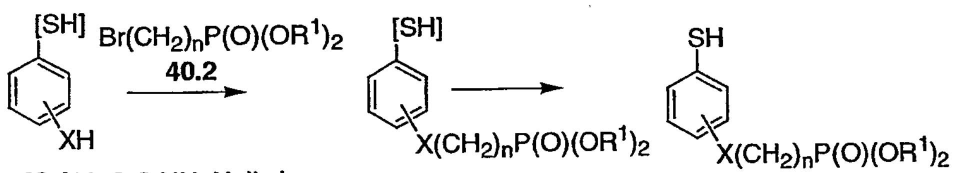
Example



39.5 **39.6** **39.8** **39.9**

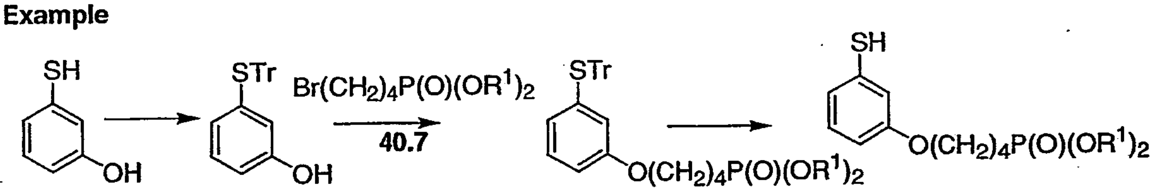
Scheme 40

Method



40.1 X=O,S,NH, Nalkyl **40.3** **40.4**

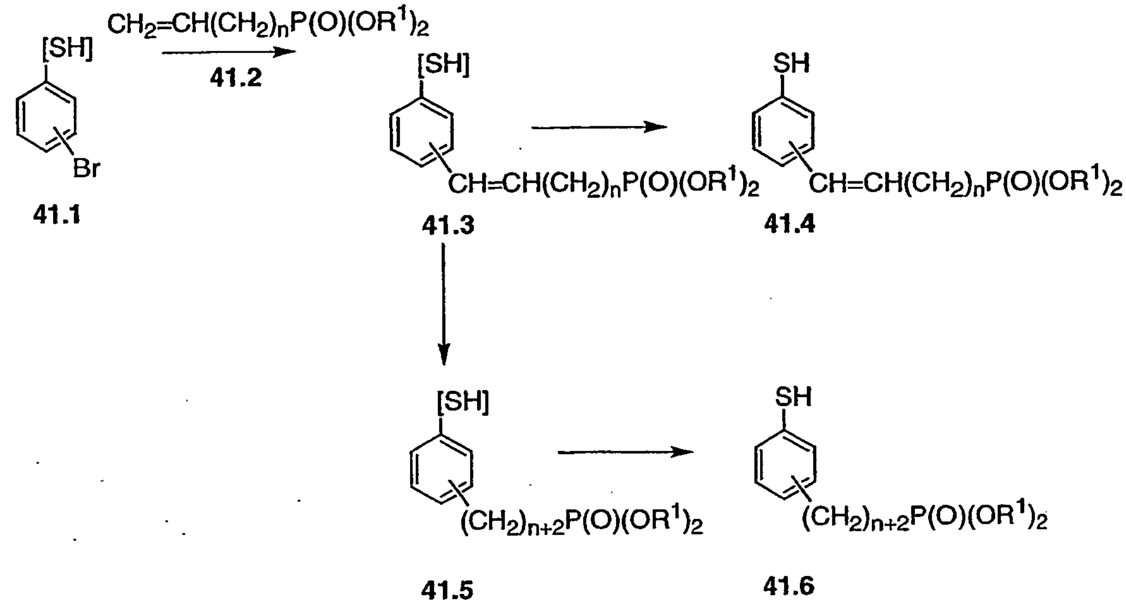
Example



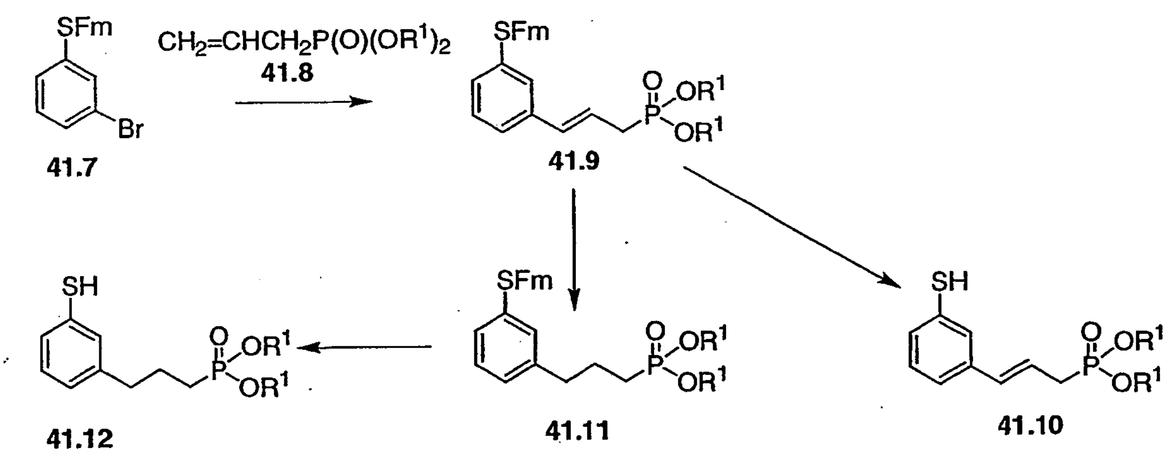
40.5 **40.6** Tr=triphenylmethyl **40.8** **40.9**

Scheme 41

Method

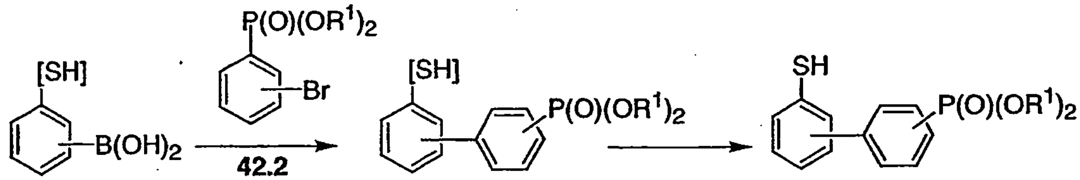


Example



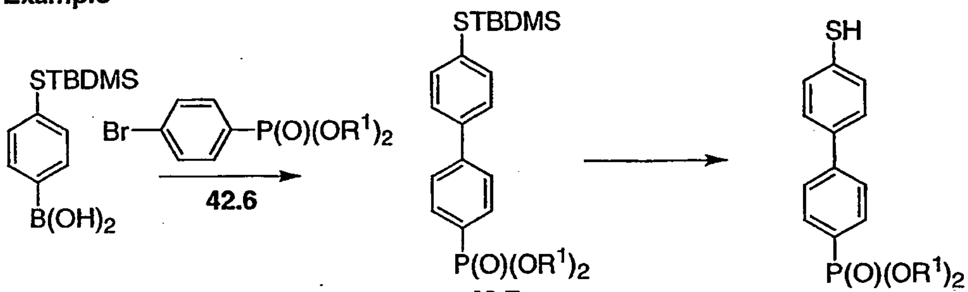
Scheme 42

Method



42.1 **42.3** **42.4**

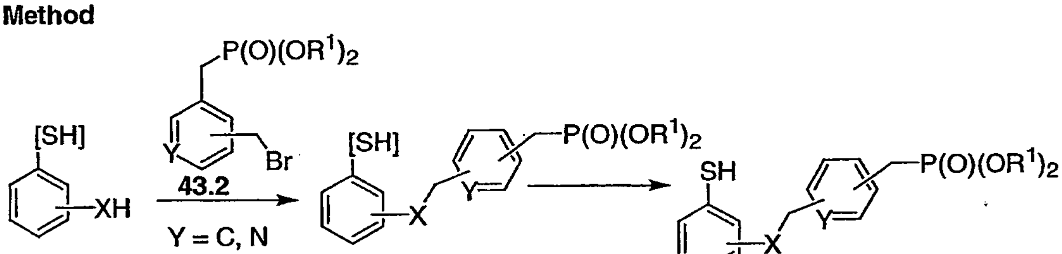
Example



42.5 **42.7** **42.8**

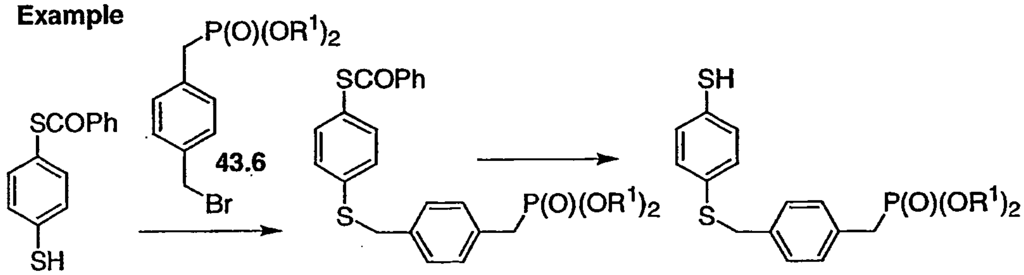
Scheme 43

Method



43.1 X =O, S, NH, Nalkyl **43.3** **43.4**

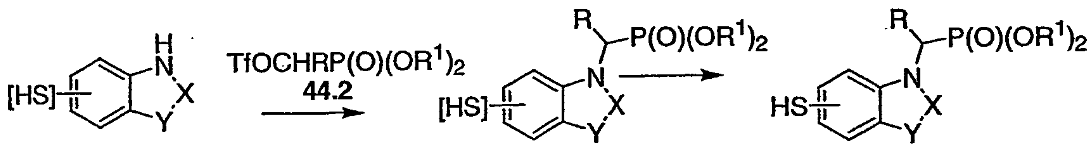
Example



43.5 **43.7** **43.8**

Scheme 44

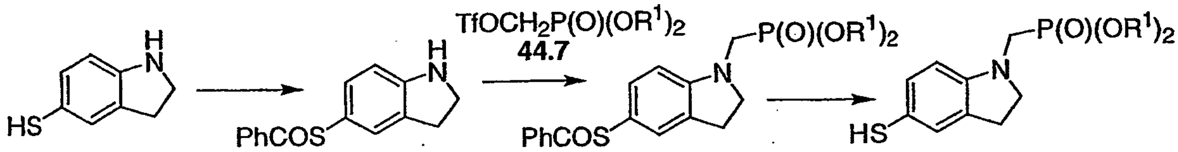
Method



44.1 44.3 44.4

X-Y = $(CH_2)_{2,3}$; CH=CH

Example



44.5 44.6 44.8 44.9

Preparation of tert-butylamine derivatives incorporating phosphonate groups.

Scheme **45** describes the preparation of tert-butylamines in which the phosphonate moiety is directly attached to the tert-butyl group. A suitably protected 2.2-dimethyl-2-aminoethyl bromide **45.1** is reacted with a trialkyl phosphite **45.2**, under the conditions of the Arbuzov reaction, as described above, to afford the phosphonate **45.3**, which is then deprotected as described previously to give **45.4**

For example, the cbz derivative of 2,2-dimethyl-2-aminoethyl bromide **45.6**, is heated with a trialkyl phosphite at ca 150°C to afford the product **45.7**. Deprotection, as previously described, then affords the free amine **45.8.**

Using the above procedures, but employing different trisubstituted phosphites, there are obtained the corresponding amines **45.4.**

Scheme **46** illustrates the preparation of phosphonate esters attached to the tert butylamine by means of a heteroatom and a carbon chain. An optionally protected alcohol or thiol **46.1** is reacted with a bromoalkylphosphonate **46.2,** to afford the displacement product **46.3.** Deprotection, if needed, then yields the amine **46.4.**

For example, the cbz derivative of 2-amino-2,2-dimethylethanol **46.5** is reacted with a dialkyl 4-bromobutyl phosphonate **46.6**, prepared as described in Synthesis, 1994, 9, 909, in

dimethylformamide containing potassium carbonate and potassium iodide, at ca 60°C to afford the phosphonate **46.7** Deprotection then affords the free amine **46.8.**
Using the above procedures, but employing different alcohols or thiols **46.1**, and/or different bromoalkylphosphonates **46.2**, there are obtained the corresponding products **46.4**.

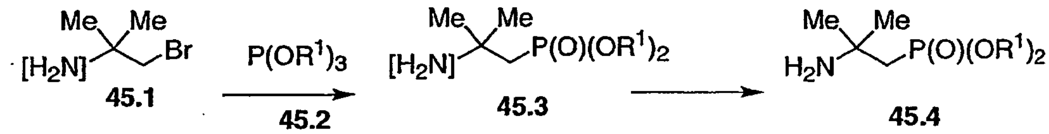
Scheme **47** describes the preparation of carbon-linked phosphonate tert butylamine derivatives, in which the carbon chain can be unsaturated or saturated.
In the procedure, a terminal acetylenic derivative of tert-butylamine **47.1** is reacted, under basic conditions, with a dialkyl chlorophosphite **47.2**, as described above in the preparation of **36.5**, (Scheme **36**). The coupled product **47.3** is deprotected to afford the amine **47.4.** Partial or complete catalytic hydrogenation of this compound affords the olefinic and saturated products **47.5** and **47.6** respectively.
For example, 2-amino-2-methylprop-1-yne **47.7**, the preparation of which is described in WO 9320804, is converted into the N-phthalimido derivative **47.8**, by reaction with phthalic anhydride, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 358. This compound is reacted with lithium diisopropylamide in tetrahydrofuran at -78°C. The resultant anion is then reacted with a dialkyl chlorophosphite **47.2** to afford the phosphonate **47.9**. Deprotection, for example by treatment with hydrazine, as described in J. Org. Chem., 43, 2320, 1978, then affords the free amine **47.10**. Partial catalytic hydrogenation, for example using Lindlar catalyst, as described in Reagents for Organic Synthesis, by L. F. Fieser and M. Fieser, Volume 1, p 566, produces the olefinic phosphonate **47.11**, and conventional catalytic hydrogenation, as described in Organic Functional Group Preparations, by S.R. Sandler and W. Karo, Academic Press, 1968, p3. for example using 5% palladium on carbon as catalyst, affords the saturated phosphonate **47.12.**
Using the above procedures, but employing different acetylenic amines **47.1**, and/or different dialkyl halophosphites, there are obtained the corresponding products **47.4, 47.5** and **47.6.**

Scheme **48** illustrates the preparation of a tert butylamine phosphonate in which the phosphonate moiety is attached by means of a cyclic amine.
In this method, an aminoethyl-substituted cyclic amine **48.1** is reacted with a limited amount of a bromoalkyl phosphonate **48.2**, using, for example, the conditions described above for the preparation of **40.3**, (Scheme **40**) to afford the displacement product **48.3**.

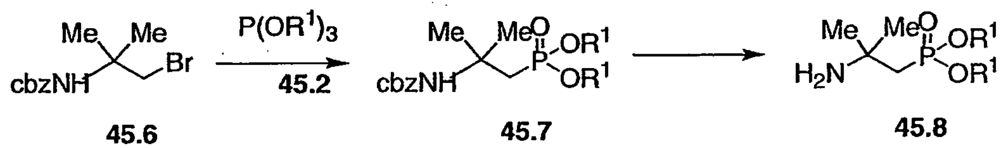
For example, 3-(1-amino-1-methyl)ethylpyrrolidine **48.4**, the preparation of which is described in Chem. Pharm. Bull., 1994, 42, 1442, is reacted with a dialkyl 4-bromobutyl phosphonate **48.5**, prepared as described in Synthesis, 1994, 9, 909, to afford the displacement product **48.6**.

Using the above procedures, but employing different cyclic amines **48.1**, and/or different bromoalkylphosphonates **48.2**, there are obtained the corresponding products **48.3**.

Scheme 45
Method

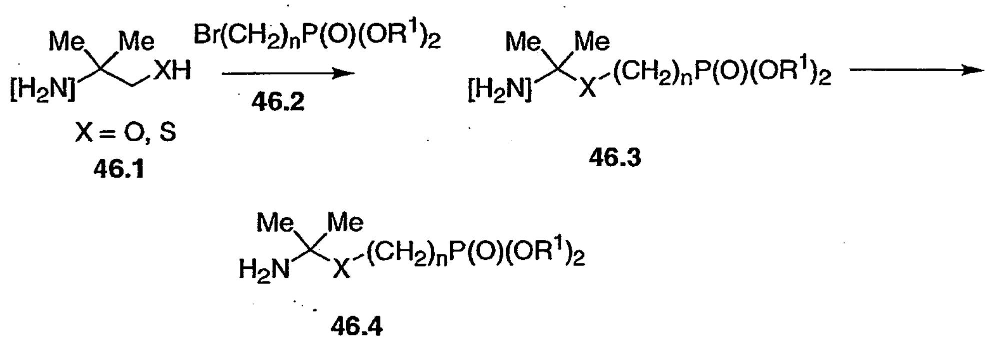


Example

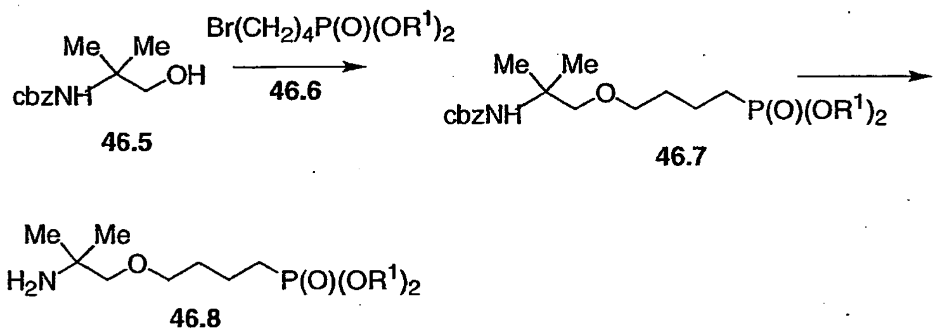


Scheme 46

Method

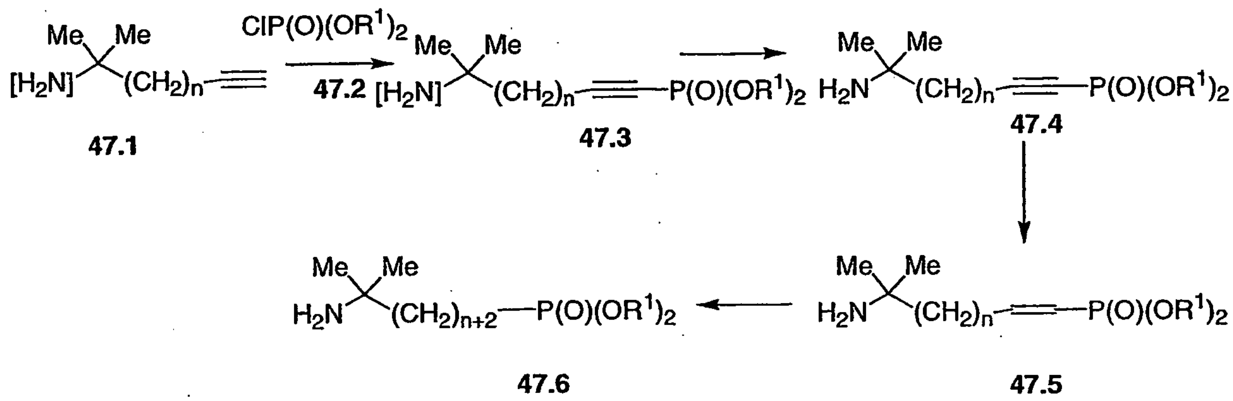


Example

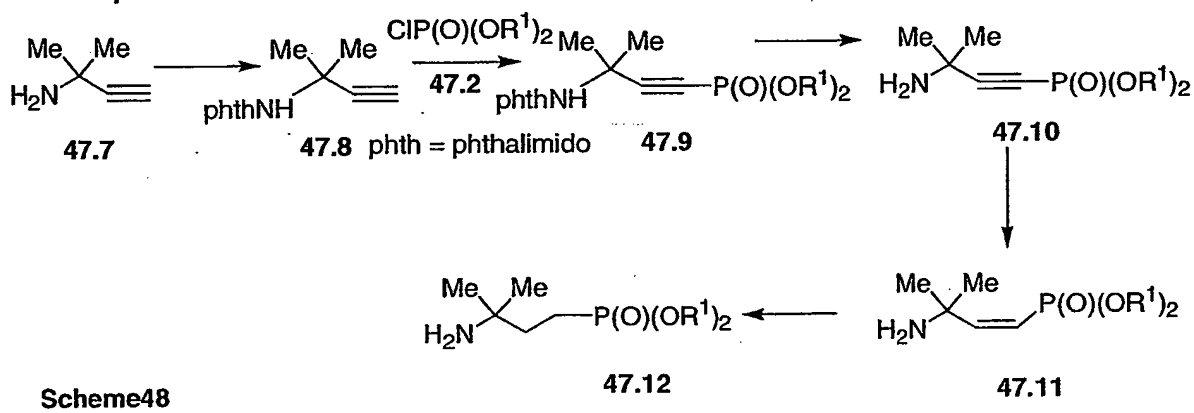


Scheme 47

Method

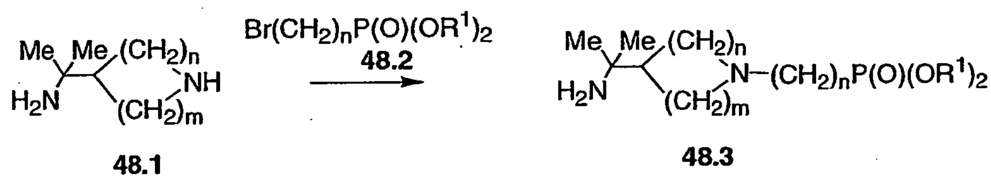


Example

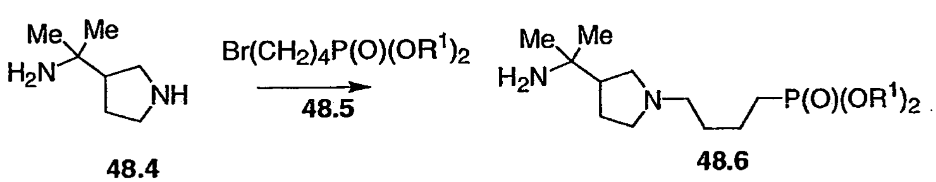


Scheme48

Method



Example



Preparation of decahydroquinolines with phosphonate moieties at the 6-position.

Scheme **48a** illustrates methods for the synthesis of intermediates for the preparation of decahydroquinolines with phosphonate moieties at the 6-position. Two methods for the preparation of the intermediate **48a.4** are shown.

In the first route, 2-hydroxy-6-methylphenylalanine **48a.1**, the preparation of which is described in J. Med. Chem., 1969, 12, 1028, is converted into the protected derivative **48a.2**. For example, the carboxylic acid is first transformed into the benzyl ester, and the product is reacted with acetic anhydride in the presence of an organic base such as, for example, pyridine, to afford the product **48a.2**, in which R is benzyl. This compound is reacted with a brominating agent, for example N-bromosuccinimide, to effect benzylic bromination and yield the product **48a.3**. The reaction is conducted in an aprotic solvent such as, for example, ethyl acetate or carbon tetrachloride, at reflux. The brominated compound **48a.3** is then treated with acid, for example dilute hydrochloric acid, to effect hydrolysis and cyclization to afford the tetrahydroisoquinoline **48a.4**, in which R is benzyl.

Alternatively, the tetrahydroisoquinoline **48a.4** can be obtained from 2-hydroxyphenylalanine **48a.5**, the preparation of which is described in Can. J. Bioch., 1971, 49, 877. This compound is subjected to the conditions of the Pictet-Spengler reaction, for example as described in Chem. Rev., 1995, 95, 1797.

Typically, the substrate **48a.5** is reacted with aqueous formaldehyde, or an equivalent such as paraformaldehyde or dimethoxymethane, in the presence of hydrochloric acid, for example as described in J. Med. Chem., 1986, 29, 784, to afford the tetrahydroisoquinoline product **48a.4**, in which R is H. Catalytic hydrogenation of the latter compound, using, for example, platinum as catalyst, as described in J. Amer. Chem. Soc., 69, 1250, 1947, or using rhodium on alumina as catalyst, as described in J. Med. Chem., 1995, 38, 4446, then gives the hydroxy-substituted decahydroisoquinoline **48a.6**. The reduction can also be performed electrochemically, as described in Trans SAEST 1984, 19, 189.

For example, the tetrahydroisoquinoline **48a.4** is subjected to hydrogenation in an alcoholic solvent, in the presence of a dilute mineral acid such as hydrochloric acid, and 5% rhodium on alumina as catalyst. The hydrogenation pressure is ca. 750 psi, and the reaction is conducted at ca 50°C, to afford the decahydroisoquinoline **48a.6**.

Protection of the carboxyl and NH groups present in **48a.6** for example by conversion of the carboxylic acid into the trichloroethyl ester, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and conversion of the NH into the N-cbz group, as described above, followed by oxidation, using, for example, pyridinium chlorochromate and the like, as described in Reagents for Organic Synthesis, by L. F. Fieser and M. Fieser, Volume 6, p. 498, affords the protected ketone **48a.9**, in which R is trichloroethyl and R_1 is cbz. Reduction of the ketone, for example by the use of sodium borohydride, as described in J. Amer. Chem. Soc., 88, 2811, 1966, or lithium tri-tertiary butyl aluminum hydride, as described in J. Amer. Chem. Soc., 80, 5372, 1958, then affords the alcohol **48a.10**.

For example, the ketone is reduced by treatment with sodium borohydride in an alcoholic solvent such as isopropanol, at ambient temperature, to afford the alcohol **48a.10**.

The alcohol **48a.6** can be converted into the thiol **48a.13** and the amine **48a.14**, by means of displacement reactions with suitable nucleophiles, with inversion of stereochemistry. For example, the alcohol **48a.6** can be converted into an activated ester such as the trifluoromethanesulfonyl ester or the methanesulfonate ester **48a.7**, by treatment with methanesulfonyl chloride and a base. The mesylate **48a.7** is then treated with a sulfur nucleophile, for example potassium thioacetate, as described in Tet. Lett., 1992, 4099, or sodium thiophosphate, as described in Acta Chem. Scand., 1960, 1980, to effect displacement of the mesylate, followed by mild basic hydrolysis, for example by treatment with aqueous ammonia, to afford the thiol **48a.13**.

For example, the mesylate **48a.7** is reacted with one molar equivalent of sodium thioacetate in a polar aprotic solvent such as, for example, dimethylformamide, at ambient temperature, to afford the thioacetate **48a.12**, in which R is $COCH_3$. The product then treated with, a mild base such as, for example, aqueous ammonia, in the presence of an organic co-solvent such as ethanol, at ambient temperature, to afford the thiol **48a.13**.

The mesylate **48a.7** can be treated with a nitrogen nucleophile, for example sodium phthalimide or sodium bis(trimethylsilyl)amide, as described in Comprehensive Organic Transformations, by R. C. Larock, p. 399, followed by deprotection as described previously, to afford the amine **48a.14**.

For example, the mesylate **48a.7** is reacted, as described in Angew. Chem. Int. Ed., 7, 919, 1968, with one molar equivalent of potassium phthalimide, in a dipolar aprotic solvent, such

as, for example, dimethylformamide, at ambient temperature, to afford the displacement product **48a.8**, in which NR^aR^b is phthalimido. Removal of the phthalimido group, for example by treatment with an alcoholic solution of hydrazine at ambient temperature, as described in J. Org. Chem., 38, 3034, 1973, then yields the amine **48a.14**. The application of the procedures described above for the conversion of the β-carbinol **48a.6** to the α-thiol **48a.13** and the α-amine **48a.14** can also be applied to the α-carbinol **48a.10**, so as to afford the β-thiol and β-amine, **48a.11**.

Scheme **49** illustrates the preparation of compounds in which the phosphonate moiety is attached to the decahydroisoquinoline by means of a heteroatom and a carbon chain. In this procedure, an alcohol, thiol or amine **49.1** is reacted with a bromoalkyl phosphonate **49.2**, under the conditions described above for the preparation of the phosphonate **40.3** (Scheme **40**), to afford the displacement product **49.3**. Removal of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described below, (Scheme **53**) then yields the amine **49.8**. For example, the compound **49.5**, in which the carboxylic acid group is protected as the trichloroethyl ester, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and the amine is protected as the cbz group, is reacted with a dialkyl 3-bromopropylphosphonate, **49.6**, the preparation of which is described in J. Amer. Chem. Soc., 2000, 122, 1554 to afford the displacement product **49.7**. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described below, (Scheme **53**) then yields the amine **49.8**. Using the above procedures, but employing, in place of the α-thiol **49.5**, the alcohols, thiols or amines **48a.6, 48a.10, 48a.11, 48a.13, 48a.14**, of either α- or β-orientation, there are obtained the corresponding products **49.4**, in which the orientation of the side chain is the same as that of the O, N or S precursors.

Scheme **50** illustrates the preparation of phosphonates linked to the decahydroisoquinoline moiety by means of a nitrogen atom and a carbon chain. The compounds are prepared by means of a reductive amination procedure, for example as described in Comprehensive Organic Transformations, by R. C. Larock, p. 421.

In this procedure, the amines **48a.14** or **48a.11** are reacted with a phosphonate aldehyde **50.1**, in the presence of a reducing agent, to afford the alkylated amine **50.2**. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described below, (Scheme **53**) then yields the amine **50.3**.

For example, the protected amino compound **48a.14** is reacted with a dialkyl formylphosphonate **50.4**, the preparation of which is described in U.S. Patent 3,784,590, in the presence of sodium cyanoborohydride, and a polar organic solvent such as ethanolic acetic acid, as described in Org. Prep. Proc. Int., 11, 201, 1979, to give the amine phosphonate **50.5**. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described below, (Scheme **53**) then yields the amine **50.6**.

Using the above procedures, but employing, instead of the α-amine **48a.14**, the β isomer, **48a.11** and/or different aldehydes **50.1**, there are obtained the corresponding products **50.3**, in which the orientation of the side chain is the same as that of the amine precursor.

Scheme **51** depicts the preparation of a decahydroisoquinoline phosphonate in which the phosphonate moiety is linked by means of a sulfur atom and a carbon chain.

In this procedure, a thiol phosphonate **51.2** is reacted with a mesylate **51.1**, to effect displacement of the mesylate group with inversion of stereochemistry, to afford the thioether product **51.3**. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme **53**) then yields the amine **51.4**.

For example, the protected mesylate **51.5** is reacted with an equimolar amount of a dialkyl 2-mercaptoethyl phosphonate **51.6**, the preparation of which is described in Aust. J. Chem., 43, 1123, 1990. The reaction is conducted in a polar organic solvent such as ethanol, in the presence of a base such as, for example, potassium carbonate, at ambient temperature, to afford the thio ether phosphonate **51.7**. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme **53**) then yields the amine **51.8**

Using the above procedures, but employing, instead of the phosphonate **51.6**, different phosphonates **51.2**, there are obtained the corresponding products **51.4**.

Scheme **52** illustrates the preparation of decahydroisoquinoline phosphonates **52.4** in which the phosphonate group is linked by means of an aromatic or heteroaromatic ring. The

compounds are prepared by means of a displacement reaction between hydroxy, thio or amino substituted substrates **52.1** and a bromomethyl substituted phosphonate **52.2**. The reaction is performed in an aprotic solvent in the presence of a base of suitable strength, depending on the nature of the reactant **52.1**. If X is S or NH, a weak organic or inorganic base such as triethylamine or potassium carbonate can be employed. If X is O, a strong base such as sodium hydride or lithium hexamethyldisilylazide is required. The displacement reaction affords the ether, thioether or amine compounds **52.3**. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described below, (Scheme **53**) then yields the amine **52.4**.

For example, the protected alcohol **52.5** is reacted at ambient temperature with a dialkyl 3-bromomethyl phenylmethylphosphonate **52.6**, the preparation of which is described above, (Scheme **43**). The reaction is conducted in a dipolar aprotic solvent such as, for example, dioxan or dimethylformamide. The solution of the carbinol is treated with one equivalent of a strong base, such as, for example, lithium hexamethyldisilylazide, and to the resultant mixture is added one molar equivalent of the bromomethyl phosphonate **52.6**, to afford the product **52.7**. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described below, (Scheme **53**) then yields the amine **52.8**.

Using the above procedures, but employing, instead of the β-carbinol **52.5**, different carbinols, thiols or amines **52.1**, of either α- or β-orientation, and/or different phosphonates **52.2**, in place of the phosphonate **52.6**, there are obtained the corresponding products **52.4** in which the orientation of the side-chain is the same as that of the starting material **52.1**.

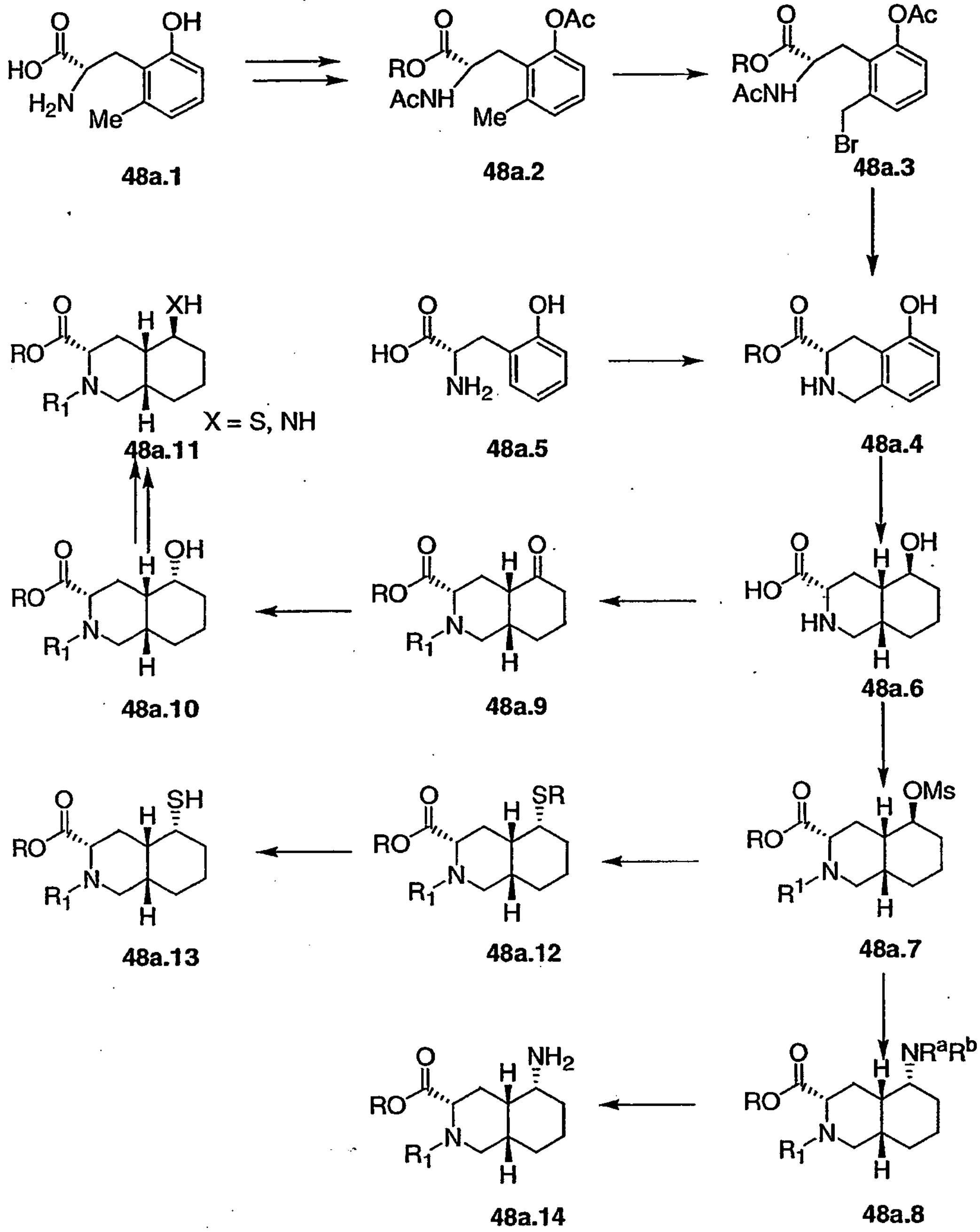
Schemes **49-52** illustrate the preparation of decahydroisoquinoline esters incorporating a phosphonate group linked to the decahydroisoquinoline nucleus.

Scheme **53** illustrates the conversion of the latter group of compounds **53.1** (in which the group B is link-$P(O)(OR^1)_2$ or optionally protected precursor substituents thereto, such as, for example, OH, SH, NH_2) to the corresponding R^4NH amides **53.5**.

As shown in Scheme **53**, the ester compounds **53.1** are deprotected to form the corresponding carboxylic acids **53.2**. The methods employed for the deprotection are chosen based on the nature of the protecting group R, the nature of the N-protecting group R^2, and the nature of the substituent at the 6-position. For example, if R is trichloroethyl, the ester group is removed by treatment with zinc in acetic acid, as described in J. Amer. Chem. Soc., 88, 852, 1966.

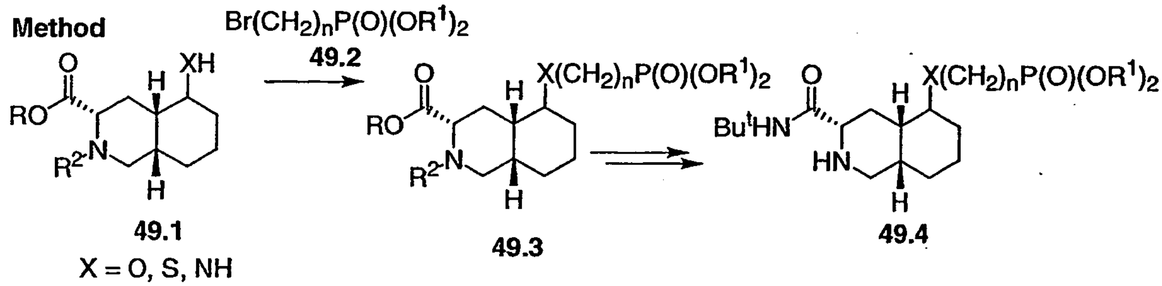
Conversion of the carboxylic acid **53.2** to the R^4NH amide **53.4** is then accomplished by reaction of the carboxylic acid, or an activated derivative thereof, with the amine R^4NH_2 **53.3** to afford the amide **53.4**, using the conditions described above for the preparation of the amide **1.6**. Deprotection of the NR^2 group, as described above, then affords the free amine **53.5**.

Scheme 48a. Intermediates for the preparation of phosphonate-containing decahydroisoquinolines.

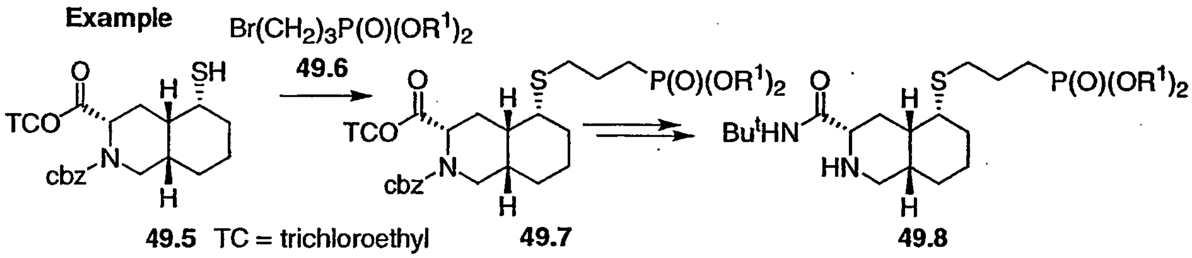


Scheme 49

Method

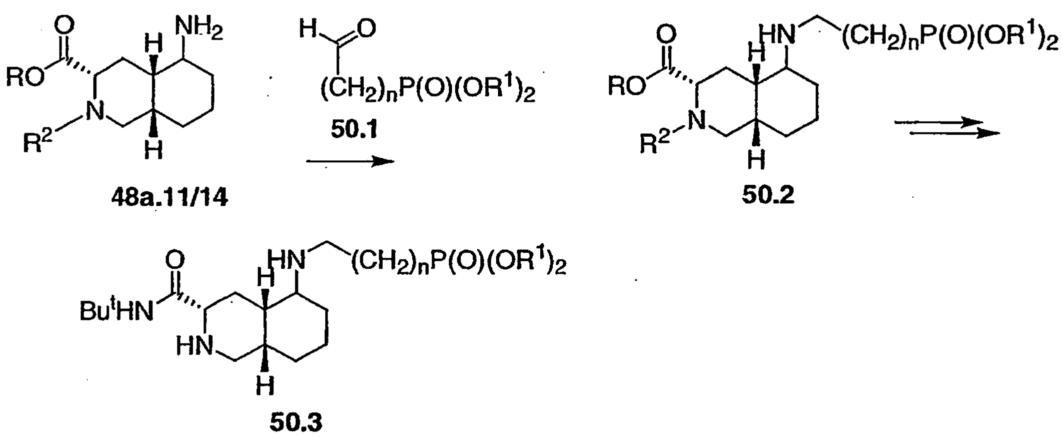


Example

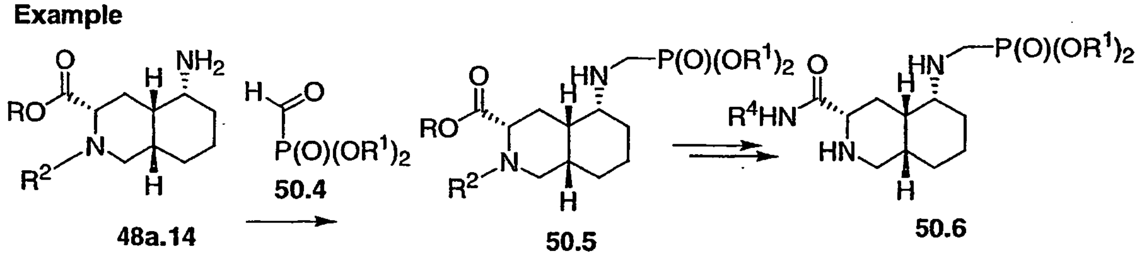


Scheme 50

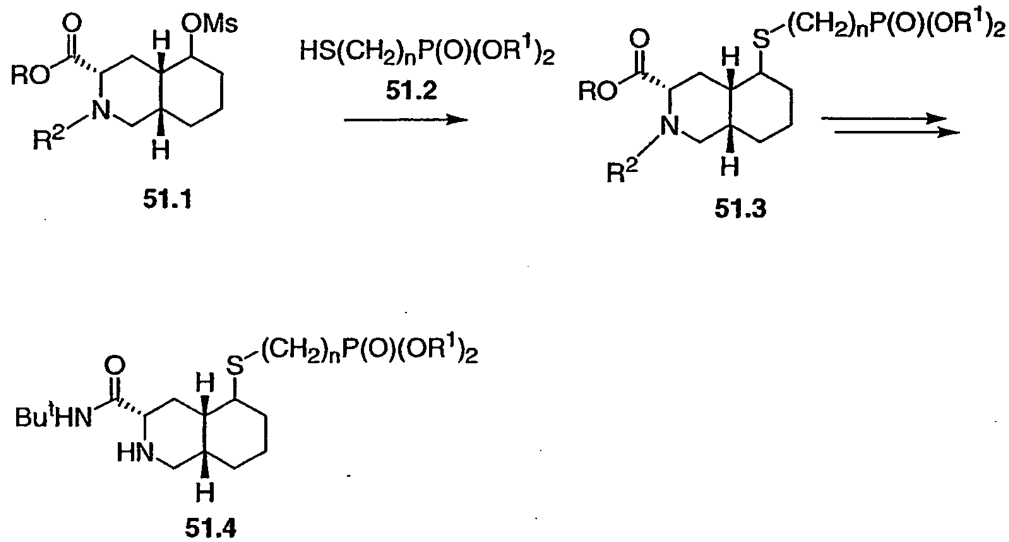
Method



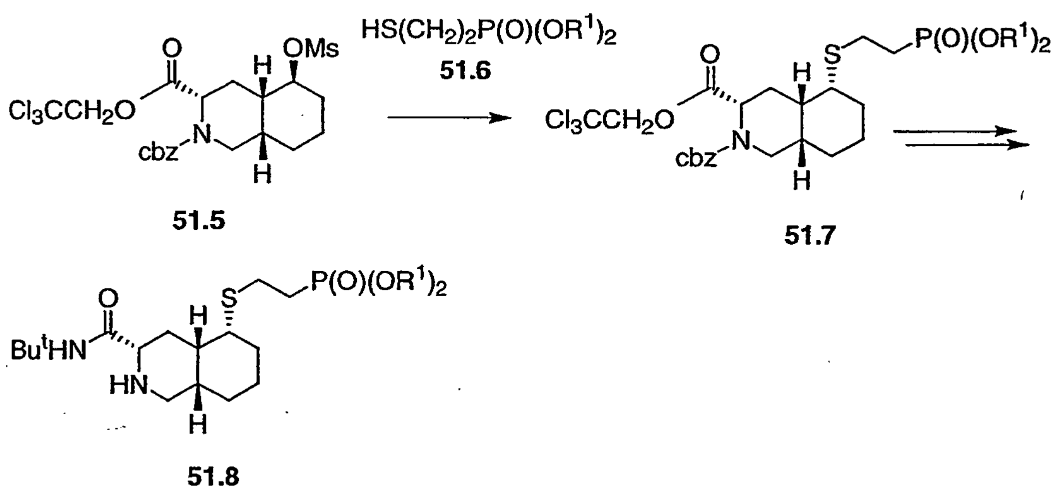
Example



Scheme 51
Method

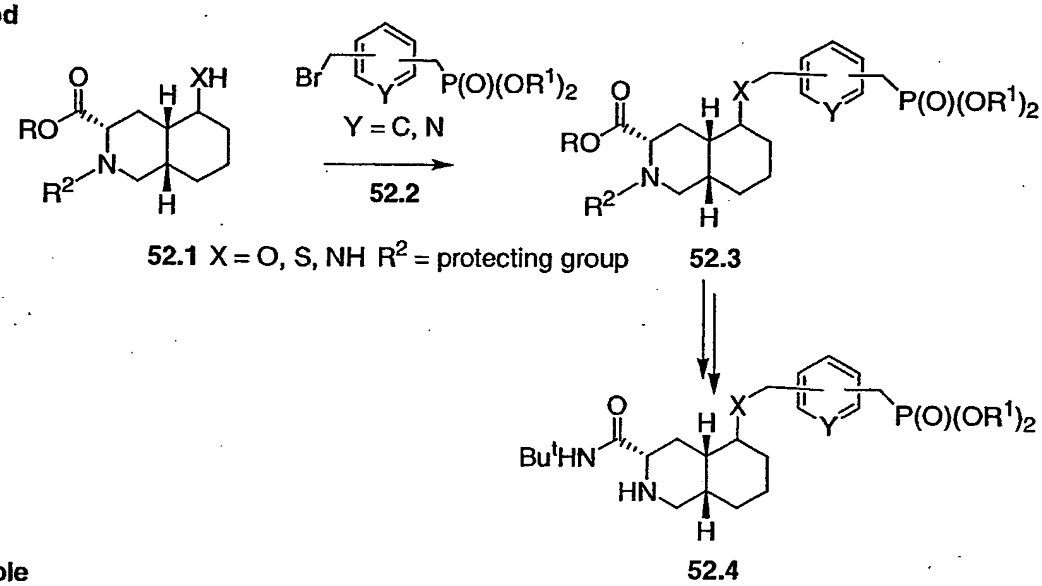


Example

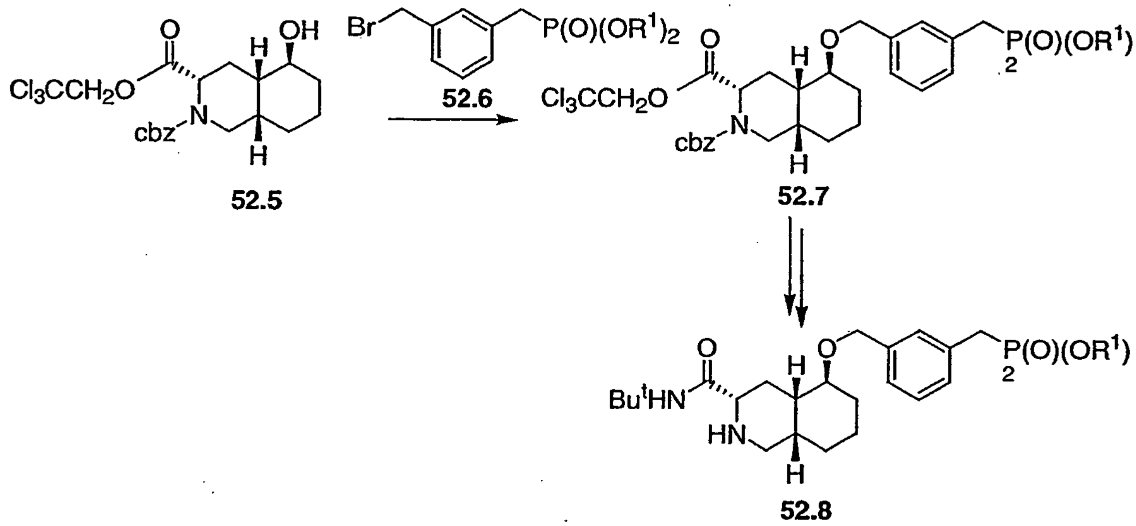


Scheme 52

Method

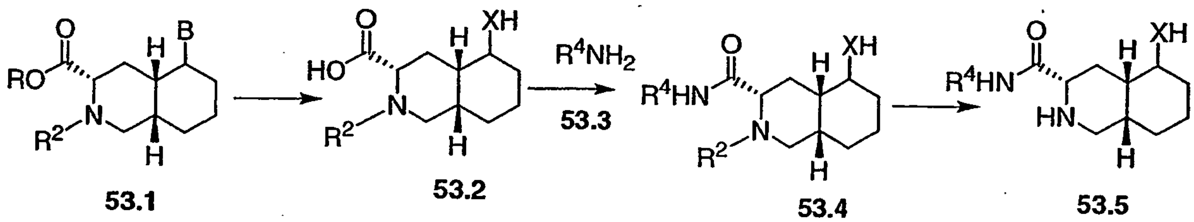


Example

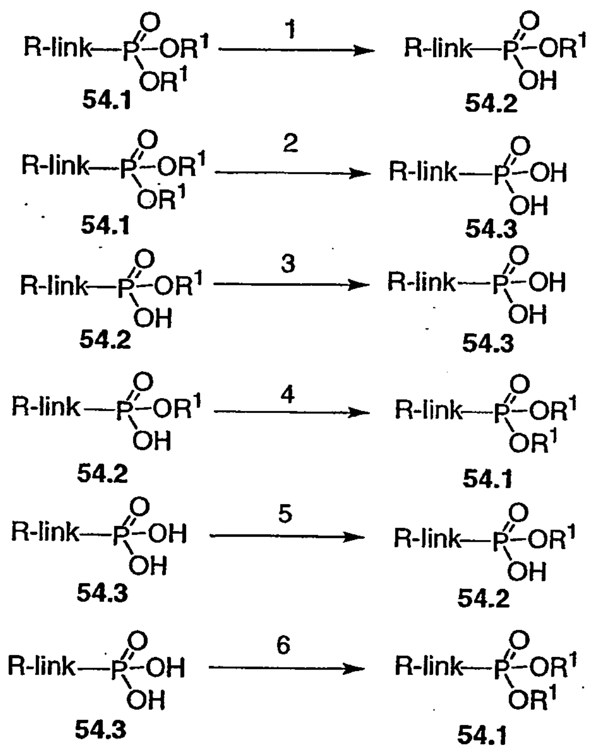


Scheme 53

Method



Scheme 54



Interconversions of the phosphonates R-link-P(O)(OR^1)$_2$, R-link-P(O)(OR^1)(OH) and R-link-P(O)(OH)$_2$.

Schemes **1 - 69** described the preparations of phosphonate esters of the general structure R-link-P(O)(OR^1)$_2$, in which the groups R^1, the structures of which are defined in Chart **1**, may be the same or different. The R^1 groups attached to a phosphonate esters **1-6**, or to precursors thereto, may be changed using established chemical transformations. The

interconversions reactions of phosphonates are illustrated in Scheme 54. The group R in Scheme 54 represents the substructure to which the substituent link-$P(O)(OR^1)_2$ is attached, either in the compounds 1-6 or in precursors thereto. The R^1 group may be changed, using the procedures described below, either in the precursor compounds, or in the esters 1-6. The methods employed for a given phosphonate transformation depend on the nature of the substituent R^1. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester 54.1 into the corresponding phosphonate monoester 54.2 (Scheme 54, Reaction 1) can be accomplished by a number of methods. For example, the ester 54.1 in which $R^1$is an aralkyl group such as benzyl, can be converted into the monoester compound 54.2 by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in J. Org. Chem., 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°C. The conversion of the diester 54.1 in which $R^1$is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester 54.2 can be effected by treatment of the ester 54.1 with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran. Phosphonate diesters 54.1 in which one of the groups $R^1$is aralkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters 54.2 in which $R^1$is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups $R^1$are alkenyl, such as allyl, can be converted into the monoester 54.2 in which $R^1$is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in J. Org. Chem., 38 3224 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester 54.1 or a phosphonate monoester 54.2 into the corresponding phosphonic acid 54.3 (Scheme 54, Reactions 2 and 3) can effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in J. Chem. Soc., Chem. Comm., 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester 54.2 in which $R^1$is aralkyl such as benzyl, can be converted into the corresponding phosphonic acid

54.3 by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate monoester **54.2** in which $R^1$is alkenyl such as, for example, allyl, can be converted into the phosphonic acid **54.3** by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in Helv. Chim. Acta., 68, 618, 1985. Palladium catalyzed hydrogenolysis of phosphonate esters **54.1** in which $R^1$is benzyl is described in J. Org. Chem., 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters **54.1** in which $R^1$is phenyl is described in J. Amer. Chem. Soc., 78, 2336, 1956.

The conversion of a phosphonate monoester **54.2** into a phosphonate diester **54.1** (Scheme **54**, Reaction 4) in which the newly introduced R^1group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl can be effected by a number of reactions in which the substrate **54.2** is reacted with a hydroxy compound R^1OH, in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester **54.2** to the diester **54.1** can be effected by the use of the Mitsonobu reaction, as described above (Scheme 25). The substrate is reacted with the hydroxy compound R^1OH, in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester **54.2** can be transformed into the phosphonate diester **54.1**, in which the introduced R^1 group is alkenyl or aralkyl, by reaction of the monoester with the halide R^1Br, in which R^1 is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the phosphonate diester in a two step procedure. In the first step, the phosphonate monoester **54.2** is transformed into the chloro analog $RP(O)(OR^1)Cl$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $RP(O)(OR^1)Cl$ is

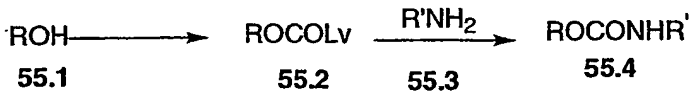
then reacted with the hydroxy compound R^1OH, in the presence of a base such as triethylamine, to afford the phosphonate diester **54.1**.

A phosphonic acid R-link-$P(O)(OH)_2$ can be transformed into a phosphonate monoester $RP(O)(OR^1)(OH)$ (Scheme **54**, Reaction 5) by means of the methods described above of for the preparation of the phosphonate diester R-link-$P(O)(OR^1)_2$ **54.1**, except that only one molar proportion of the component R^1OH or R^1Br is employed.

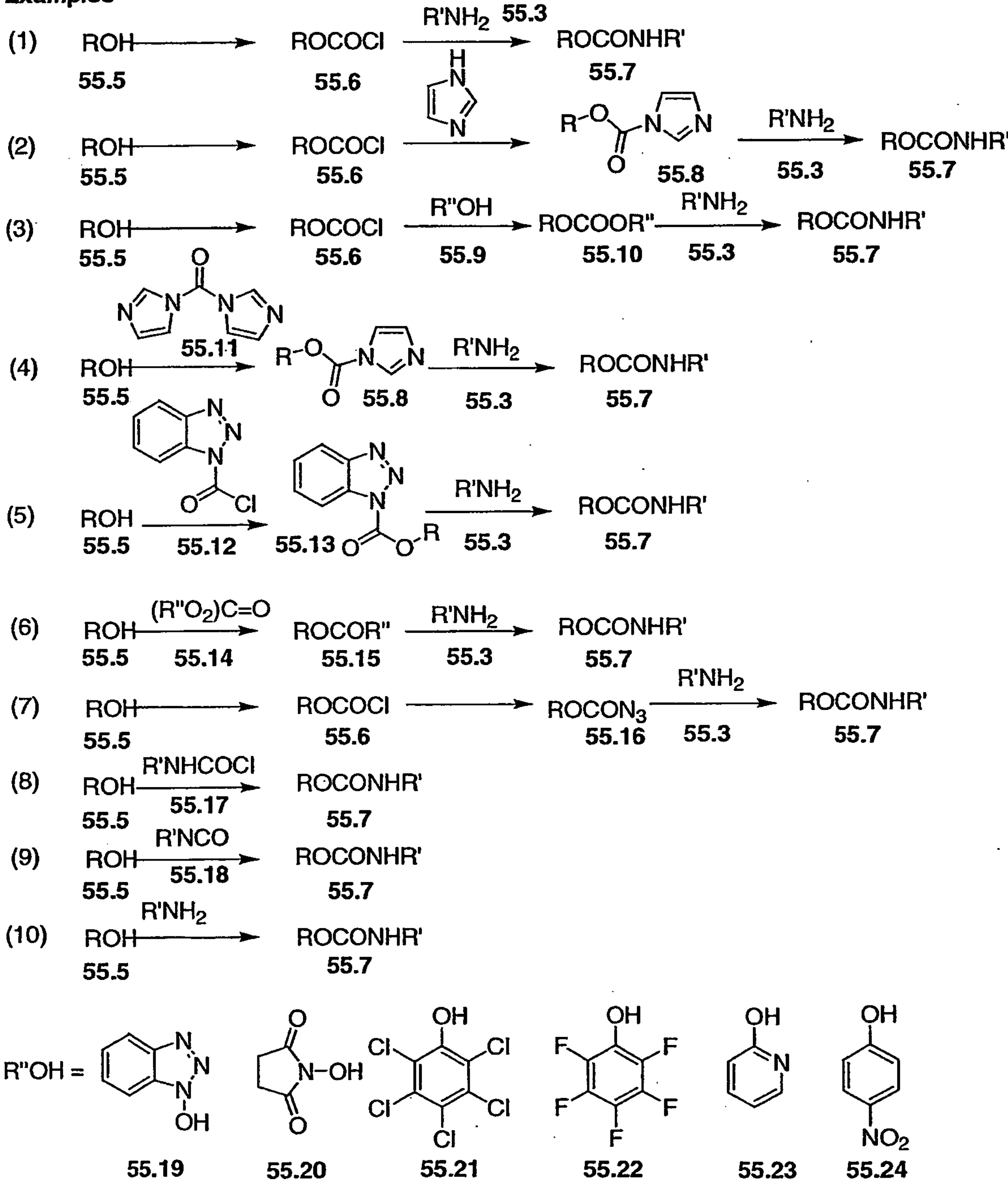
A phosphonic acid R-link-$P(O)(OH)_2$ **54.3** can be transformed into a phosphonate diester R-link-$P(O)(OR^1)_2$ **54.1** (Scheme **54**, Reaction 6) by a coupling reaction with the hydroxy compound R^1OH, in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids **54.3** can be transformed into phosphonic esters **54.1** in which R^1 is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca 70°C. Alternatively, phosphonic acids **54.3** can be transformed into phosphonic esters **54.1** in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester **54.1**.

Scheme 55

General reaction



Examples



Preparation of the phosphonate esters 1-6 incorporating carbamate moieties.

The phosphonate esters **1-6** in which the R^6CO group is formally derived from the carboxylic acid synthons **C39 - C49** as shown in Chart **2c**, contain a carbamate moiety. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations, A. R. Katritzky, ed., Pergamon, 1995, Vol. 6, p. 416ff, and in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p. 260ff.

Scheme **55** illustrates various methods by which the carbamate linkage can be synthesized. As shown in Scheme **55**, in the general reaction generating carbamates, a carbinol **55.1** is converted into the activated derivative **55.2** in which Lv is a leaving group such as halo, imidazolyl, benztriazolyl and the like, as described below. The activated derivative **55.2** is then reacted with an amine **55.3**, to afford the carbamate product **55.4**. Examples **1 – 7** in Scheme **55** depict methods by which the general reaction can be effected. Examples **8 - 10** illustrate alternative methods for the preparation of carbamates.

Scheme **55**, Example 1 illustrates the preparation of carbamates employing a chloroformyl derivative of the carbinol **55.5**. In this procedure, the carbinol **55.5** is reacted with phosgene, in an inert solvent such as toluene, at about 0°C, as described in Org. Syn. Coll. Vol. 3, 167, 1965, or with an equivalent reagent such as trichloromethoxy chloroformate, as described in Org. Syn. Coll. Vol. 6, 715, 1988, to afford the chloroformate **55.6**. The latter compound is then reacted with the amine component **55.3**, in the presence of an organic or inorganic base, to afford the carbamate **55.7**. For example, the chloroformyl compound **55.6** is reacted with the amine **55.3** in a water-miscible solvent such as tetrahydrofuran, in the presence of aqueous sodium hydroxide, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to yield the carbamate **55.7**. Alternatively, the reaction is preformed in dichloromethane in the presence of an organic base such as diisopropylethylamine or dimethylaminopyridine.

Scheme **55**, Example **2** depicts the reaction of the chloroformate compound **55.6** with imidazole, **55.7**, to produce the imidazolide **55.8**. The imidazolide product is then reacted with the amine **55.3** to yield the carbamate **55.7**. The preparation of the imidazolide is performed in an aprotic solvent such as dichloromethane at 0°C, and the preparation of the carbamate is conducted in a similar solvent at ambient temperature, optionally in the presence of a base such as dimethylaminopyridine, as described in J. Med. Chem., 1989, 32, 357.

Scheme 55 Example **3**, depicts the reaction of the chloroformate **55.6** with an activated hydroxyl compound R"OH, to yield the mixed carbonate ester **55.10**. The reaction is conducted in an inert organic solvent such as ether or dichloromethane, in the presence of a base such as dicyclohexylamine or triethylamine. The hydroxyl component R"OH is selected from the group of compounds **55.19** - **55.24** shown in Scheme 55, and similar compounds. For example, if the component R"OH is hydroxybenztriazole **55.19**, N-hydroxysuccinimide **55.20**, or pentachlorophenol, **55.21**, the mixed carbonate **55.10** is obtained by the reaction of the chloroformate with the hydroxyl compound in an ethereal solvent in the presence of dicyclohexylamine, as described in Can. J. Chem., 1982, 60, 976. A similar reaction in which the component R"OH is pentafluorophenol **55.22** or 2-hydroxypyridine **55.23** can be performed in an ethereal solvent in the presence of triethylamine, as described in Syn., 1986, 303, and Chem. Ber. 118, 468, 1985.

Scheme 55 Example **4** illustrates the preparation of carbamates in which an alkyloxycarbonylimidazole **55.8** is employed. In this procedure, a carbinol **55.5** is reacted with an equimolar amount of carbonyl diimidazole **55.11** to prepare the intermediate **55.8**. The reaction is conducted in an aprotic organic solvent such as dichloromethane or tetrahydrofuran. The acyloxyimidazole **55.8** is then reacted with an equimolar amount of the amine R'NH_2 to afford the carbamate **55.7**. The reaction is performed in an aprotic organic solvent such as dichloromethane, as described in Tet. Lett., 42, 2001, 5227, to afford the carbamate **55.7**.

Scheme 55, Example **5** illustrates the preparation of carbamates by means of an intermediate alkoxycarbonylbenztriazole **55.13**. In this procedure, a carbinol ROH is reacted at ambient temperature with an equimolar amount of benztriazole carbonyl chloride **55.12**, to afford the alkoxycarbonyl product **55.13**. The reaction is performed in an organic solvent such as benzene or toluene, in the presence of a tertiary organic amine such as triethylamine, as described in Syn., 1977, 704. This product is then reacted with the amine R'NH_2 to afford the carbamate **55.7**. The reaction is conducted in toluene or ethanol, at from ambient temperature to about 80°C as described in Syn., 1977, 704.

Scheme 55, Example **6** illustrates the preparation of carbamates in which a carbonate $(R"O)_2CO$, **55.14**, is reacted with a carbinol **55.5** to afford the intermediate alkyloxycarbonyl intermediate **55.15**. The latter reagent is then reacted with the amine R'NH_2 to afford the carbamate **55.7**. The procedure in which the reagent **55.15** is derived from

hydroxybenztriazole **55.19** is described in Synthesis, 1993, 908; the procedure in which the reagent **55.15** is derived from N-hydroxysuccinimide **55.20** is described in Tet. Lett., 1992, 2781; the procedure in which the reagent **55.15** is derived from 2-hydroxypyridine **55.23** is described in Tet. Lett., 1991, 4251; the procedure in which the reagent **55.15** is derived from 4-nitrophenol **55.24** is described in Syn. 1993, 103. The reaction between equimolar amounts of the carbinol ROH and the carbonate **55.14** is conducted in an inert organic solvent at ambient temperature.

Scheme **55**, Example **7** illustrates the preparation of carbamates from alkoxycarbonyl azides **55.16**. in this procedure, an alkyl chloroformate **55.6** is reacted with an azide, for example sodium azide, to afford the alkoxycarbonyl azide **55.16**. The latter compound is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate **55.7**. The reaction is conducted at ambient temperature in a polar aprotic solvent such as dimethylsulfoxide, for example as described in Syn., 1982, 404.

Scheme **55**, Example **8** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and the chloroformyl derivative of an amine. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 647, the reactants are combined at ambient temperature in an aprotic solvent such as acetonitrile, in the presence of a base such as triethylamine, to afford the carbamate **55.7**.

Scheme **55**, Example **9** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an isocyanate **55.18**. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 645, the reactants are combined at ambient temperature in an aprotic solvent such as ether or dichloromethane and the like, to afford the carbamate **55.7**.

Scheme **55**, Example **10** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an amine $R'NH_2$. In this procedure, which is described in Chem. Lett. 1972, 373, the reactants are combined at ambient temperature in an aprotic organic solvent such as tetrahydrofuran, in the presence of a tertiary base such as triethylamine, and selenium. Carbon monoxide is passed through the solution and the reaction proceeds to afford the carbamate **55.7**.

Preparation of phosphonate intermediates 5 and 6 with phosphonate moieties incorporated into the group R^6COOH and $R^2NHCH(R^3)CONHR^4$.

The chemical transformations described in Schemes **1 - 55** illustrate the preparation of compounds **1-4** in which the phosphonate ester moiety is attached to the quinoline-2-carboxylate substructure, (Schemes **1-8**), the phenylalanine or thiophenol moiety (Schemes **9-13**), the tert-butylamine moiety (Schemes **14-18**) and the decahydroisoquinoline moiety (Schemes **19 - 22**).

The various chemical methods employed herein (Schemes **25 - 69**)for the preparation of phosphonate groups can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate ester groups into the compounds R^6COOH, as defined in Charts **3a**, **3b** and **3c**, and into the compounds $R^2NHCH(R^3)CONHR^4$ as defined in Chart **2**. For example, Schemes **56 - 61** illustrate the preparation of phosphonate-containing analogs of the phenoxyacetic acid **C8** (Chart **3a**), Schemes **62 - 65** illustrate the preparation of phosphonate-containing analogs of the carboxylic acid **C4**, Schemes **66 - 69** illustrate the preparation of phosphonate-containing analogs of the amine **A12** (Chart **2**), and Schemes **70-75** illustrate the preparation of phosphonate-containing analogs of the carboxylic acid **C38**. The resultant phosphonate-containing analogs $R^{6a}COOH$ and $R^{2a}NHCH(R^{3a})CONHR^4$ can then, using the procedures described above, be employed in the preparation of the compounds **5** and **6**. The procedures required for the introduction of the phosphonate-containing analogs $R^{6a}COOH$ and $R^{2a}NHCH(R^{3a})CONHR^4$ are the same as those described above for the introduction of the R^6CO and $R^2NHCH(R^3)CONHR^4$ moieties.

Preparation of dimethylphenoxyacetic acids incorporating phosphonate moieties.

Scheme **56** illustrates two alternative methods by means of which 2,6-dimethylphenoxyacetic acids bearing phosphonate moieties may be prepared. The phosphonate group may be introduced into the 2,6-dimethylphenol moiety, followed by attachment of the acetic acid group, or the phosphonate group may be introduced into a preformed 2,6-dimethylphenoxyacetic acid intermediate. In the first sequence, a substituted 2,6-dimethylphenol **56.1**, in which the substituent B is a precursor to the group link-$P(O)(OR^1)_2$, and in which the phenolic hydroxyl may or may not be protected, depending on the reactions to be performed, is converted into a phosphonate-containing compound **56.2**. Methods for

the conversion of the substituent B into the group link-$P(O)(OR^1)_2$ are described in Schemes **25 - 69**.

The protected phenolic hydroxyl group present in the phosphonate-containing product **56.2** is then deprotected, using methods described below, to afford the phenol **56.3**.

The phenolic product **56.3** is then transformed into the corresponding phenoxyacetic acid **56.4**, in a two step procedure. In the first step, the phenol **56.3** is reacted with an ester of bromoacetic acid **56.5**, in which R is an alkyl group or a protecting group. Methods for the protection of carboxylic acids are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff. The alkylation of phenols to afford phenolic ethers is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 446ff. Typically, the phenol and the alkylating agent are reacted together in the presence of an organic or inorganic base, such as, for example, diazabicyclononene, (DBN) or potassium carbonate, in a polar organic solvent such as, for example, dimethylformamide or acetonitrile.

Preferably, equimolar amounts of the phenol **56.3** and ethyl bromoacetate are reacted together in the presence of cesium carbonate, in dioxan at reflux temperature, for example as described in U.S. Patent 5,914,332, to afford the ester **56.6**.

The thus-obtained ester **56.6** is then hydrolyzed to afford the carboxylic acid **56.4**. The methods used for this reaction depend on the nature of the group R. If R is an alkyl group such as methyl, hydrolysis can be effected by treatment of the ester with aqueous or aqueous alcoholic base, or by use of an esterase enzyme such as porcine liver esterase. If R is a protecting group, methods for hydrolysis are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff.

Preferably, the ester product **56.6** which R is ethyl is hydrolyzed to the carboxylic acid **56.4** by reaction with lithium hydroxide in aqueous methanol at ambient temperature, as described in U.S. Patent 5,914,332.

Alternatively, an appropriately substituted 2,6-dimethylphenol **56.7**, in which the substituent B is a precursor to the group link-$P(O)(OR^1)_2$, is transformed into the corresponding phenoxyacetic ester **56.8**. The conditions employed for the alkylation reaction are similar to those described above for the conversion of the phenol **56.3** into the ester **56.6**.

The phenolic ester **56.8** is then converted, by transformation of the group B into the group link-$P(O)(OR^1)_2$ followed by ester hydrolysis, into the carboxylic acid **56.4**. The group B

which is present in the ester **56.4** may be transformed into the group link-$P(O)(OR^1)_2$ either before or after hydrolysis of the ester moiety into the carboxylic acid group, depending on the nature of the chemical transformations required.

Schemes **56** - **61** illustrate the preparation of 2,6-dimethylphenoxyacetic acids incorporating phosphonate ester groups. The procedures shown can also be applied to the preparation of phenoxyacetic esters acids **56.8**, with, if appropriate, modifications made according to the knowledge of one skilled in the art.

Scheme **57** illustrates the preparation of 2,6-dimethylphenoxyacetic acids incorporating a phosphonate ester which is attached to the phenolic group by means of a carbon chain incorporating a nitrogen atom. The compounds **57.4** are obtained by means of a reductive alkylation reaction between a 2,6-dimethylphenol aldehyde **57.1** and an aminoalkyl phosphonate ester **57.2**. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 421. In this procedure, the amine component **57.2** and the aldehyde component **57.1** are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride or diisobutylaluminum hydride, to yield the amine product **57.3**. The amination product **57.3** is then converted into the phenoxyacetic acid compound **57.4**, using the alkylation and ester hydrolysis procedures described above, (Scheme **56**)

For example, equimolar amounts of 4-hydroxy-3,5-dimethylbenzaldehyde **57.5** (Aldrich) and a dialkyl aminoethyl phosphonate **57.6**, the preparation of which is described in J. Org. Chem., 2000, 65, 676, are reacted together in the presence of sodium cyanoborohydride and acetic acid, as described, for example, in J. Amer. Chem. Soc., 91, 3996, 1969, to afford the amine product **57.3**. The product is then converted into the acetic acid **57.8**, as described above.

Using the above procedures, but employing, in place of the aldehyde **57.5**, different aldehydes **57.1**, and/or different aminoalkyl phosphonates **57.2**, the corresponding products **57.4** are obtained.

In this and succeeding examples, the nature of the phosphonate ester group can be varied, either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described above (Scheme **54**)

Scheme **58** depicts the preparation of 2,6-dimethylphenols incorporating a phosphonate group linked to the phenyl ring by means of a saturated or unsaturated alkylene chain. In this procedure, an optionally protected bromo-substituted 2,6-dimethylphenol **58.1** is coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenyl phosphonate **58.2**. The coupling of aryl bromides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) or palladium (2) catalyst. Following the coupling reaction, the product **58.3** is converted, using the procedures described above, (Scheme **56**) into the corresponding phenoxyacetic acid **58.4**. Alternatively, the olefinic product **58.3** is reduced to afford the saturated 2,6-dimethylphenol derivative **58.5**. Methods for the reduction of carbon-carbon double bonds are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 6. The methods include catalytic reduction, or chemical reduction employing, for example, diborane or diimide. Following the reduction reaction, the product **58.5** is converted, as described above, (Scheme **56**) into the corresponding phenoxyacetic acid **58.6**.

For example, 3-bromo-2,6-dimethylphenol **58.7**, prepared as described in Can. J. Chem., 1983, 61, 1045, is converted into the tert-butyldimethylsilyl ether **58.8**, by reaction with chloro-tert-butyldimethylsilane, and a base such as imidazole, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990 p. 77. The product **58.8** is reacted with an equimolar amount of a dialkyl allyl phosphonate **58.9**, for example diethyl allylphosphonate (Aldrich) in the presence of ca. 3 mol % of bis(triphenylphosphine) palladium(II) chloride, in dimethylformamide at ca. 60°C, to produce the coupled product **58.10**. The silyl group is removed, for example by the treatment of the ether **58.10** with a solution of tetrabutylammonium fluoride in tetrahydrofuran, as described in J. Am. Chem., Soc., 94, 6190, 1972, to afford the phenol **58.11**. This compound is converted, employing the procedures described above, (Scheme **56**) into the corresponding phenoxyacetic acid **58.12**. Alternatively, the unsaturated compound **58.11** is reduced, for example by catalytic hydrogenation employing 5% palladium on carbon as catalyst, in an alcoholic solvent such as methanol, as described, for example, in Hydrogenation Methods, by R. N. Rylander, Academic Press, 1985, Ch. 2, to afford the saturated analog **58.13**. This compound is

converted, employing the procedures described above, (Scheme **56**) into the corresponding phenoxyacetic acid **58.14**.

Using the above procedures, but employing, in place of 3-bromo-2,6-dimethylphenol **58.7**, different bromophenols **58.1**, and/or different dialkyl alkenyl phosphonates **58.2**, the corresponding products **58.4** and **58.6** are obtained.

Scheme **59** illustrates the preparation of phosphonate-containing 2,6-dimethylphenoxyacetic acids **59.1** in which the phosphonate group is attached to the 2,6-dimethylphenoxy moiety by means of a carbocyclic ring. In this procedure, a bromo-substituted 2,6-dimethylphenol **59.2** is converted, using the procedures illustrated in Scheme **56**, into the corresponding 2,6-dimethylphenoxyacetic ester **59.3**. The latter compound is then reacted, by means of a palladium-catalyzed Heck reaction, with a cycloalkenone **59.4**, in which n is 1 or 2. The coupling reaction is conducted under the same conditions as those described above for the preparation of **58.3** (Scheme **58**). The product **59.5** is then reduced catalytically, as described above for the reduction of **58.3**, (Scheme **58**), to afford the substituted cycloalkanone **59.6**. The ketone is then subjected to a reductive amination procedure, by reaction with a dialkyl 2-aminoethylphosphonate **59.7** and sodium triacetoxyborohydride, as described in J. Org. Chem., 61, 3849, 1996, to yield the amine phosphonate **59.8**. The reductive amination reaction is conducted under the same conditions as those described above for the preparation of the amine **57.3** (Scheme **57**). The resultant ester **59.8** is then hydrolyzed, as described above, to afford the phenoxyacetic acid **59.1**.

For example, 4-bromo-2,6-dimethylphenol **59.9** (Aldrich) is converted, as described above, into the phenoxy ester **59.10**. The latter compound is then coupled, in dimethylformamide solution at ca. 60°C, with cyclohexenone **59.11**, in the presence of tetrakis(triphenylphosphine)palladium(0) and triethylamine, to yield the cyclohexenone **59.12**. The enone is then reduced to the saturated ketone **59.13**, by means of catalytic hydrogenation employing 5% palladium on carbon as catalyst. The saturated ketone is then reacted with an equimolar amount of a dialkyl aminoethylphosphonate **59.14**, prepared as described in J. Org. Chem., 2000, 65, 676, in the presence of sodium cyanoborohydride, to yield the amine **59.15**. Hydrolysis, employing lithium hydroxide in aqueous methanol at ambient temperature, then yields the acetic acid **59.16**.

Using the above procedures, but employing, in place of 4-bromo-2,6-dimethylphenol **59.9**, different bromo-substituted 2,6-dimethylphenols **59.2**, and/or different cycloalkenones **59.4**, and/or different dialkyl aminoalkylphosphonates **59.7**, the corresponding products **59.1** are obtained.

Scheme **60** illustrates the preparation of 2,6-dimethylphenoxyacetic acids incorporating a phosphonate group attached to the phenyl ring by means of a heteroatom and an alkylene chain. The compounds are obtained by means of alkylation reactions in which an optionally protected hydroxy, thio or amino-substituted 2,6-dimethylphenol **60.1** is reacted, in the presence of a base such as, for example, potassium carbonate, and optionally in the presence of a catalytic amount of an iodide such as potassium iodide, with a dialkyl bromoalkyl phosphonate **60.2**. The reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile at from ambient temperature to about 80°C. The product of the alkylation reaction, **60.3** is then converted, as described above (Scheme **56**) into the phenoxyacetic acid **60.4**.

For example, 2,6-dimethyl-4-mercaptophenol **60.5**, prepared as described in EP 482342, is reacted in dimethylformamide at ca. 60°C with an equimolar amount of a dialkyl bromobutyl phosphonate **60.6**, the preparation of which is described in Synthesis, 1994, 9, 909, in the presence of ca. 5 molar equivalents of potassium carbonate, to afford the thioether product **60.7**. This compound is converted, employing the procedures described above, (Scheme **56**) into the corresponding phenoxyacetic acid **60.8**.

Using the above procedures, but employing, in place of 2,6-dimethyl-4-mercaptophenol **60.5**, different hydroxy, thio or aminophenols **60.1**, and/or different dialkyl bromoalkyl phosphonates **60.2**, the corresponding products **60.4** are obtained.

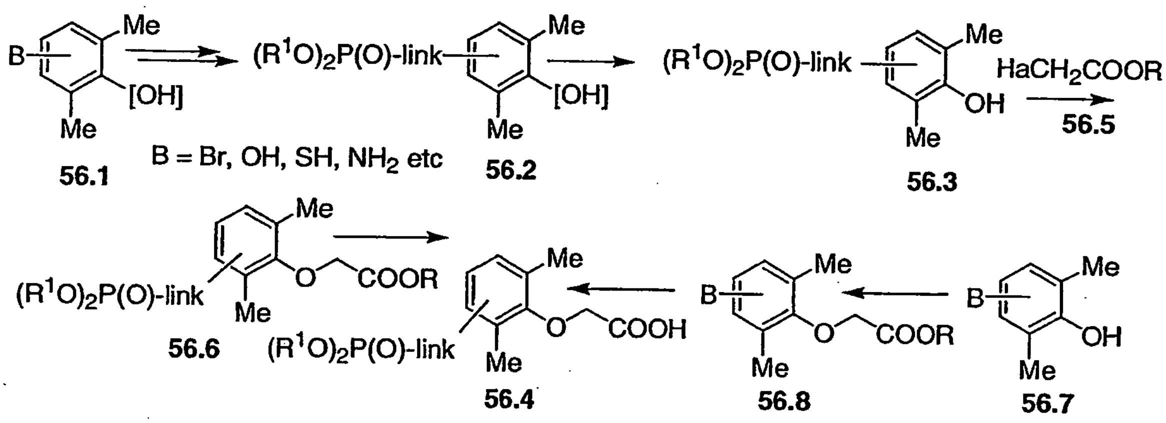
Scheme **61** illustrates the preparation of 2,6-dimethylphenoxyacetic acids incorporating a phosphonate ester group attached by means of an aromatic or heteroaromatic group. In this procedure, an optionally protected hydroxy, mercapto or amino-substituted 2.6-dimethylphenol **61.1** is reacted, under basic conditions, with a bis(halomethyl)aryl or heteroaryl compound **61.2**. Equimolar amounts of the phenol and the halomethyl compound are reacted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as potassium or cesium carbonate, or dimethylaminopyridine, to afford

the ether, thioether or amino product **61.3**. The product **61.3** is then converted, using the procedures described above, (Scheme **56**) into the phenoxyacetic ester **61.4**. The latter compound is then subjected to an Arbuzov reaction by reaction with a trialkylphosphite **61.5** at ca. 100°C to afford the phosphonate ester **61.6**. The preparation of phosphonates by means of the Arbuzov reaction is described, for example, in Handb. Organophosphorus Chem., 1992, 115. The resultant product **61.6** is then converted into the acetic acid **61.7** by hydrolysis of the ester moiety, using the procedures described above, (Scheme **56**).

For example, 4-hydroxy-2,6-dimethylphenol **61.8** (Aldrich) is reacted with one molar equivalent of 3,5-bis(chloromethyl)pyridine, the preparation of which is described in Eur. J. Inorg. Chem., 1998, 2, 163, to afford the ether **61.10**. The reaction is conducted in acetonitrile at ambient temperature in the presence of five molar equivalents of potassium carbonate. The product **61.10** is then reacted with ethyl bromoacetate, using the procedures described above, (Scheme **56**) to afford the phenoxyacetic ester **61.11**. This product is heated at 100°C for 3 hours with three molar equivalents of triethyl phosphite **61.12**, to afford the phosphonate ester **61.13**. Hydrolysis of the acetic ester moiety, as described above, for example by reaction with lithium hydroxide in aqueous ethanol, then affords the phenoxyacetic acid **61.14**.

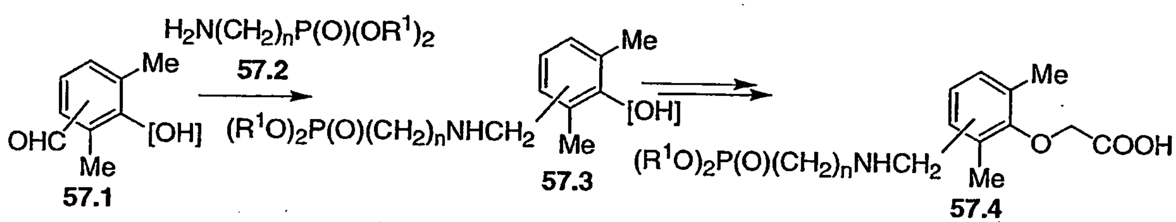
Using the above procedures, but employing, in place of the bis(chloromethyl) pyridine **61.9**, different bis(halomethyl) aromatic or heteroaromatic compounds **61.2**, and/or different hydroxy, mercapto or amino-substituted 2,6-dimethylphenols **61.1** and/or different trialkyl phosphites **61.5**, the corresponding products **61.7** are obtained.

Scheme 56

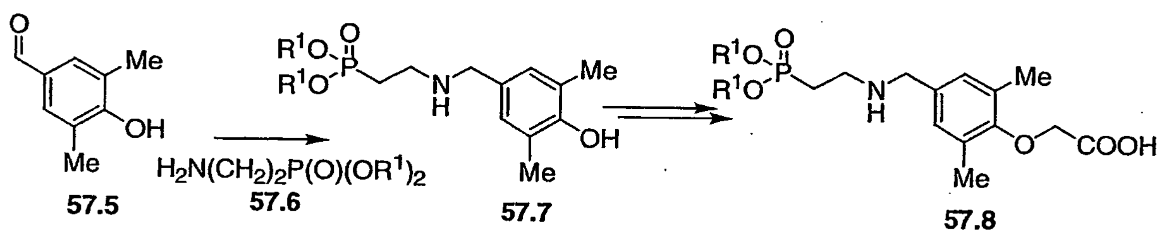


Scheme 57

Method

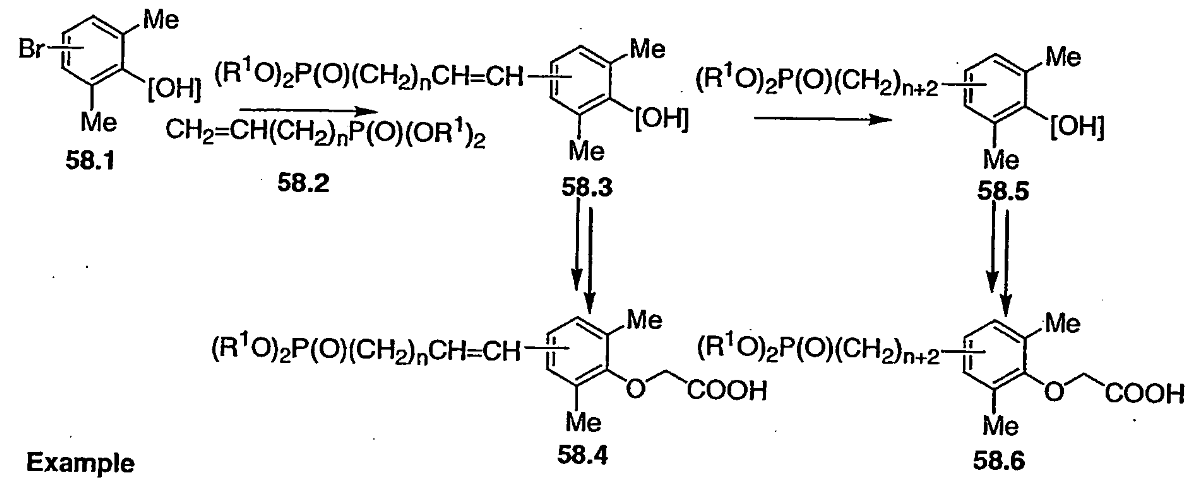


Example

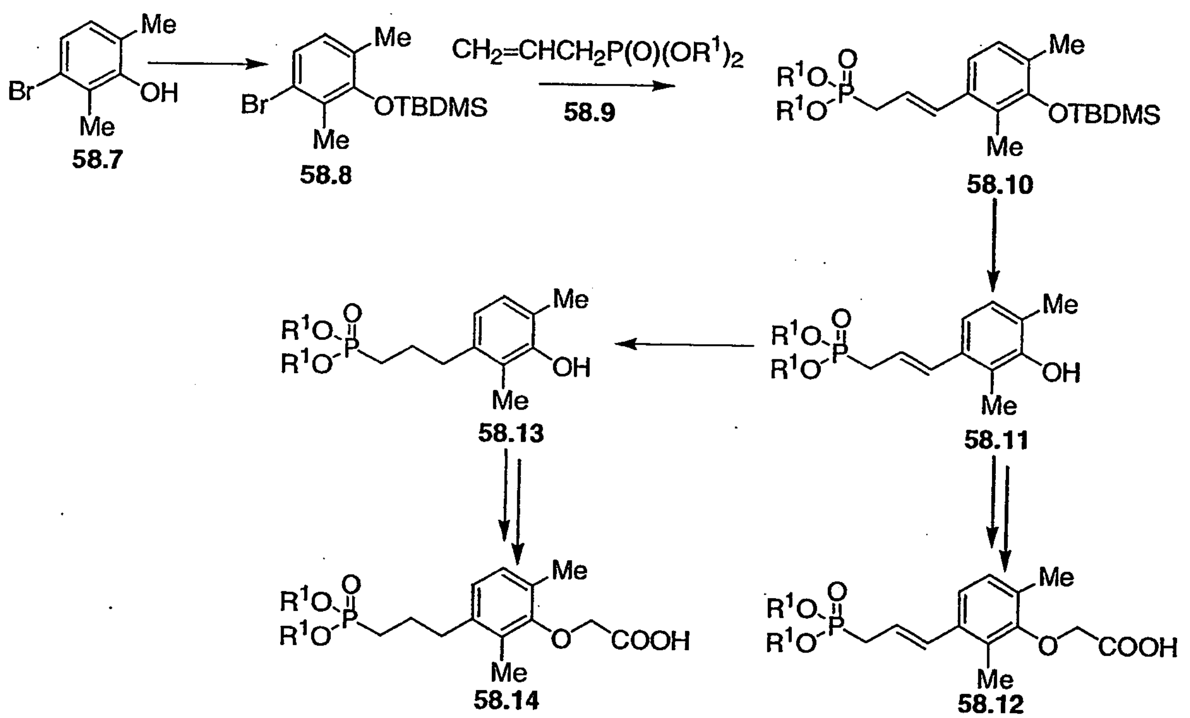


Scheme 58

Method

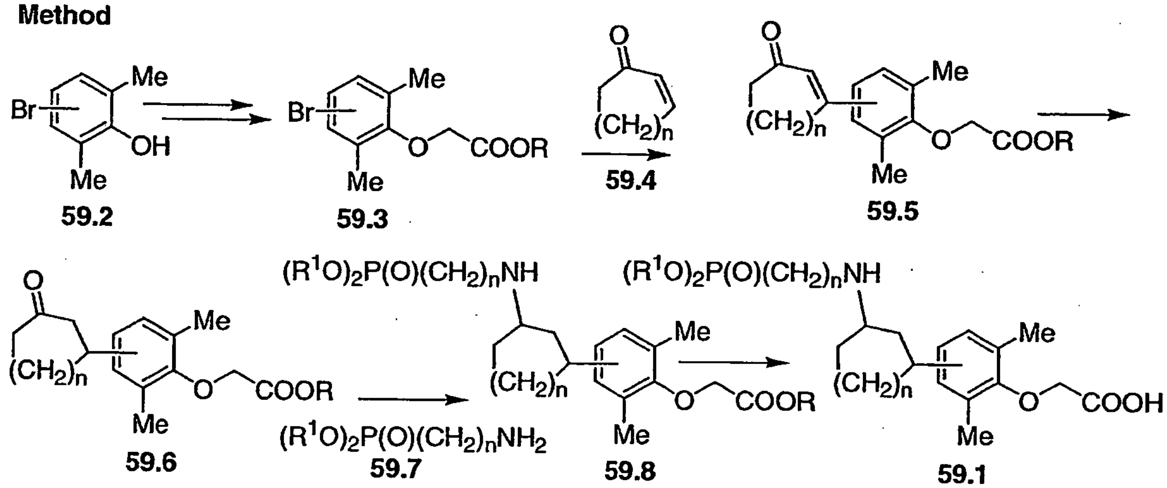


Example

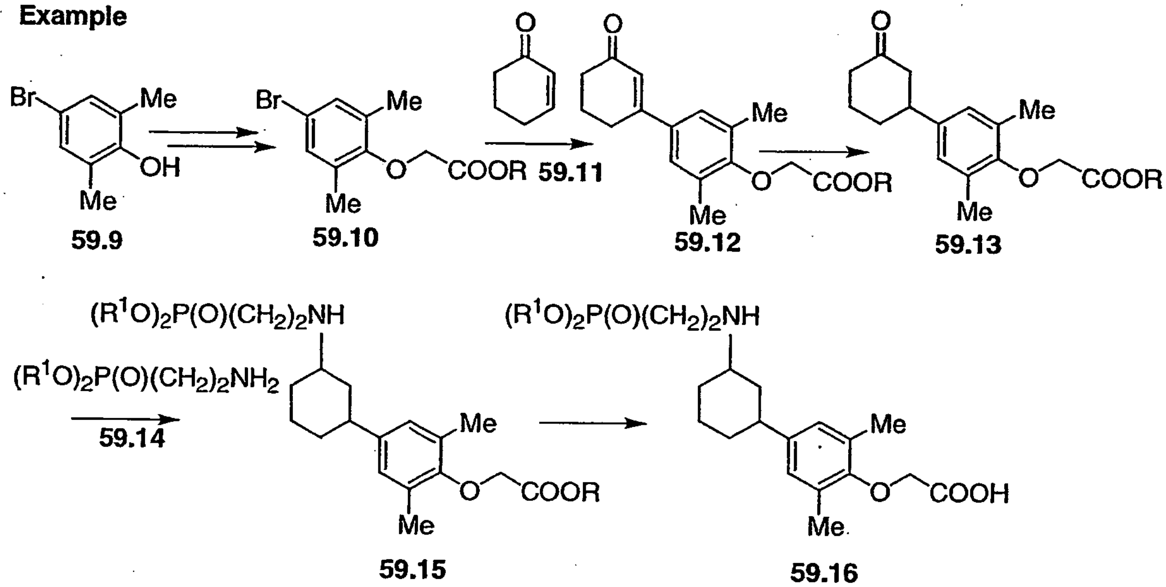


Scheme 59

Method

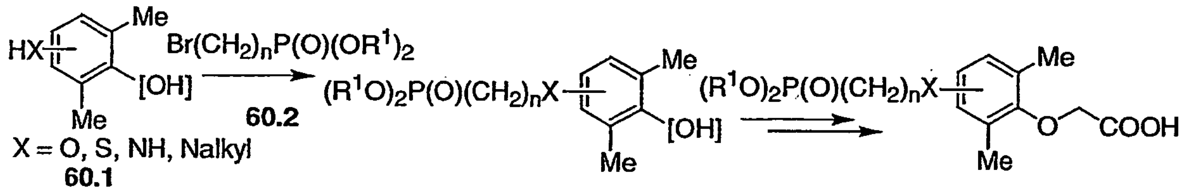


Example



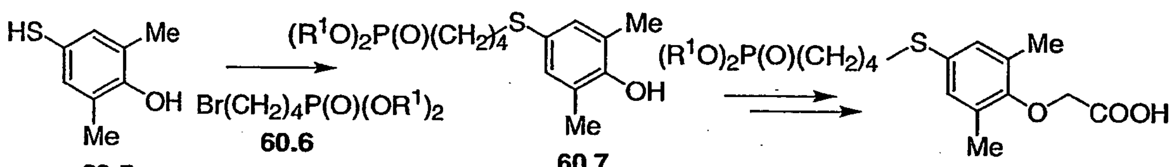
Scheme 60

Method



60.1 60.2 60.3 60.4

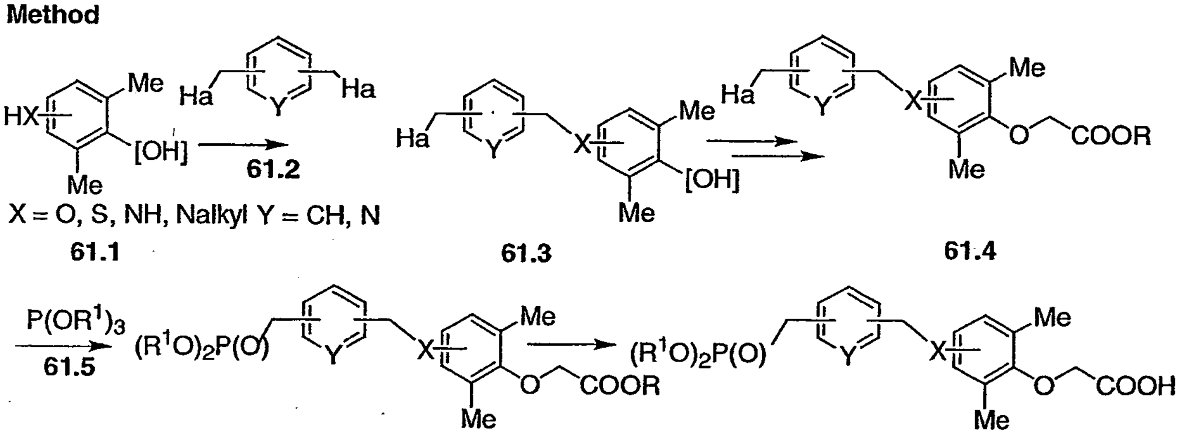
Example



60.5 60.6 60.7 60.8

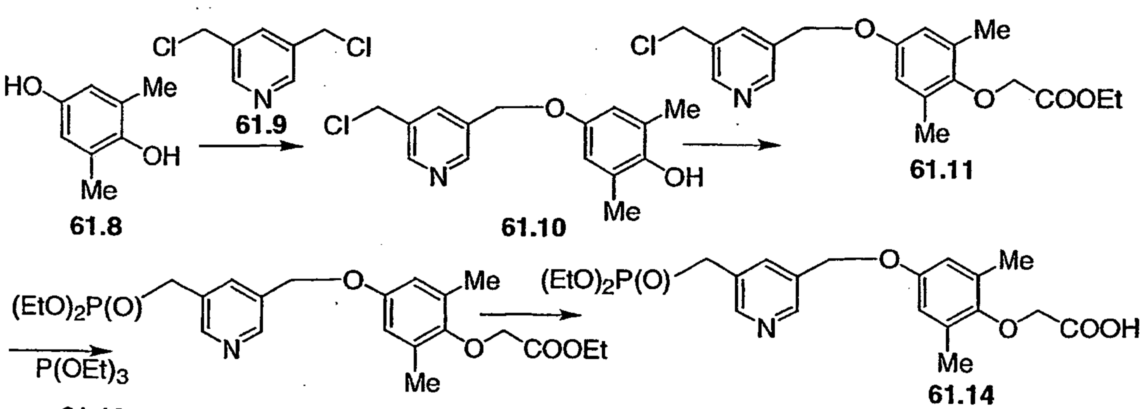
Scheme 61

Method



61.1 61.2 61.3 61.4 61.5 61.6 61.7

Example



61.8 61.9 61.10 61.11 61.12 61.13 61.14

Preparation of benzyl carbamate compounds incorporating phosphonate groups.

Scheme **62** depicts the preparation of phosphonate-containing analogs of the benzyl carbamate aminoacid derivative **C4** in which the phosphonate moiety is either directly attached to the phenyl ring or attached by means of an alkylene chain. In this procedure, a dialkyl hydroxymethylphenyl alkylphosphonate **62.1** is converted into an activated derivative **62.2**, in which Lv is a leaving group, as described above (Scheme **55**). The product is then reacted with a suitably protected aminoacid **62.3**, to afford the carbamate product **62.4**. The reaction is conducted under the conditions described above for the preparation of carbamates (Scheme 55). The protecting group on the carboxylic acid group in the product **62.4** is then removed to afford the free carboxylic acid **62.5**. Methods for the protection and deprotection of carboxylic acids are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff.

For example, as shown in Scheme **62**, Example **1**, a dialkyl 4-hydroxymethylphenyl phosphonate **62.6**, prepared as described in US 5569664, is reacted with phosgene, or an equivalent thereof, as described above (Scheme **55**), to afford the chloroformyl product **62.7**. This compound is then reacted in an inert solvent such as dichloromethane or tetrahydrofuran, with the tert. butyl aminoacid ester **62.3**, in the presence of a base such as triethylamine, to yield the carbamate product **62.8**. The conversion of acids into tert. butyl esters is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 245ff. The ester can be prepared by the reaction of the carboxylic acid with isobutylene and an acid catalyst, or by conventional esterification procedures employing tert. butanol. The tert. butyl protecting group is then removed from the product **62.8**, for example by reaction with trifluoroacetic acid at ambient temperature for about one hour, to afford the carboxylic acid **62.9**.

As a further example, Scheme **62**, Example **2** shows the conversion of a dialkyl 4-hydroxymethyl benzyl phosphonate **62.10**, prepared as described in J. Am. Chem. Soc., 1996, 118, 5881, into the hydroxybenztriazole derivative **62.11**. The reaction is performed as described above (Scheme **55**). The activated derivative is then reacted with the aminoacid

derivative **62.3**, as described above, to afford the carbamate **62.12**. deprotection, as previously described, then affords the carboxylic acid **62.13**.

Using the above procedures, but employing, in place of the phosphonates **62.6** and **62.10**, different phosphonates **62.1**, and/or different aminoacid derivatives **62.3**, the corresponding products **62.5** are obtained.

Scheme **63** depicts the preparation of phosphonate-containing analogs of the benzyl carbamate aminoacid derivative **C4** in which the phosphonate moiety is attached to the phenyl ring by means of a saturated or unsaturated alkylene chain. In this procedure, a bromo-substituted benzyl alcohol **63.1** is subjected to a palladium catalyzed Heck reaction, as described above, (Scheme **26**) with a dialkyl alkenyl phosphonate **63.2**, to afford the olefinic product **63.3**. The product is then converted into the activated derivative **63.4**, which is then reacted with aminoacid derivative **62.3**, as described above, to afford, after deprotection of the carboxyl group, the carbamate product **63.5**. Optionally, the olefinic coupling product can be reduced to the saturated analog **63.6**. The reduction reaction can be effected chemically, for example by the use of diimide or diborane, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 5. The product **63.6** is then converted, as described above, into the carbamate derivative **63.8**.

For example, 3-bromobenzyl alcohol **63.9** is coupled in acetonitrile solution, with a dialkyl allylphosphonate **63.10** (Aldrich), in the presence of palladium acetate, triethylamine and tri-o-tolylphosphine, as described in Synthesis, 1983, 556, to afford the product **63.11**. This material is then reacted with carbonyl diimidazole, as described above, (Scheme **55**) to afford the imidazolide **63.12**. The product is then coupled with the aminoacid derivative **62.3**, to afford after deprotection, the product **63.13**. Alternatively, the unsaturated phosphonate **63.11** is reduced, for example by reaction with diborane in tetrahydrofuran at ambient temperature, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 5., to afford the saturated analog **63.14**. The latter compound is then transformed, as described above, into the carbamate aminoacid derivative **63.15**.

Using the above procedures, but employing, in place of the 3-bromobenzyl alcohol **63.9**, different bromobenzyl alcohols **63.1**, and/or different alkenyl phosphonates **63.2**, and/or different amino acid derivatives, the corresponding products **63.5** and **63.8** are obtained.

Scheme **64** depicts the preparation of phosphonate-containing analogs of the benzyl carbamate aminoacid derivative **C4** in which the phosphonate moiety is attached to the phenyl ring by means of an amino-containing alkylene chain. In this procedure, a formyl-substituted benzyl alcohol **64.1** is converted, using the procedures described above is Schemes **55** and **63**, into the aminoacid carbamate derivative **64.2**. The product is then subjected to a reductive amination reaction with a dialkyl aminoalkyl phosphonate **64.3**, to afford the phosphonate product **64.4**. Reductive amination of carbonyl compounds is described above (Scheme **27**). For example, 3-formyl benzyl alcohol **64.5** is converted into the carbamate derivative **64.6**. The product is then reacted in ethanol solution at ambient temperature with a dialkyl aminoethyl phosphonate **64.7**, the preparation of which is described in J. Org. Chem., 2000, 65, 676, in the presence of sodium cyanoborohydride, to yield the phosphonate product **64.8**. Using the above procedures, but employing, in place of the 3-formylbenzyl alcohol **64.5**, different formylbenzyl alcohols **64.1**, and/or different aminoalkyl phosphonates **64.3**, the corresponding products **64.4** are obtained.

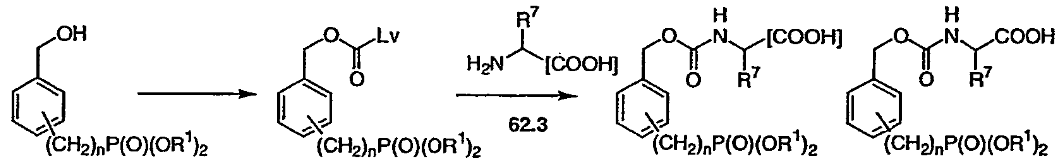
Scheme **65** depicts the preparation of phosphonate-containing analogs of the benzyl carbamate aminoacid derivative **C4** in which the phosphonate moiety is attached to the phenyl ring by means of an O, S or N-alkyl-containing alkylene chain. In this procedure, a chloromethyl-substituted benzyl alcohol **65.1** is reacted with a dialkyl hydroxy, mercapto or alkylaminoalkyl phosphonate **65.2**. The alkylation reaction is conducted between equimolar amounts of the reactants in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of an inorganic or organic base, such as diisopropylethylamine, dimethylaminopyridine, potassium carbonate and the like. The alkylated product **65.3** is then converted, as previously described, into the carbamate aminoacid derivative **65.4**.

For example, 4-chloromethylbenzyl alcohol **65.5**, (Aldrich) is reacted at ca. 60°C in acetonitrile solution with a dialkyl hydroxypropyl phosphonate **65.6**, the preparation of which is described in Zh. Obschei. Khim., 1974, 44, 1834, in the presence of dimethylaminopyridine, to afford the ether product **65.7**. The product is then converted, as previously described, into the carbamate derivative **65.8**.

Using the above procedures, but employing, in place of 4-(chloromethyl)benzyl alcohol **65.5**, different chloromethyl benzyl alcohols **65.1**, and/or different hydroxy, mercapto or alkylamino phosphonates **65.2**, the corresponding products **65.4** are obtained.

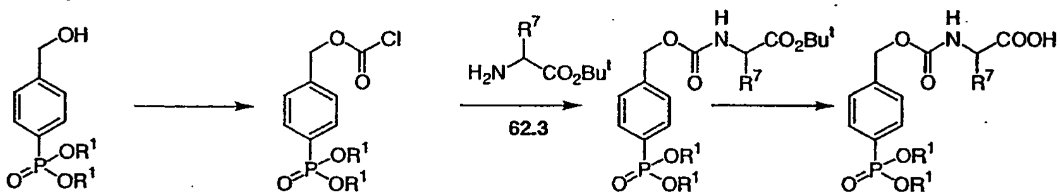
Scheme 62

Method



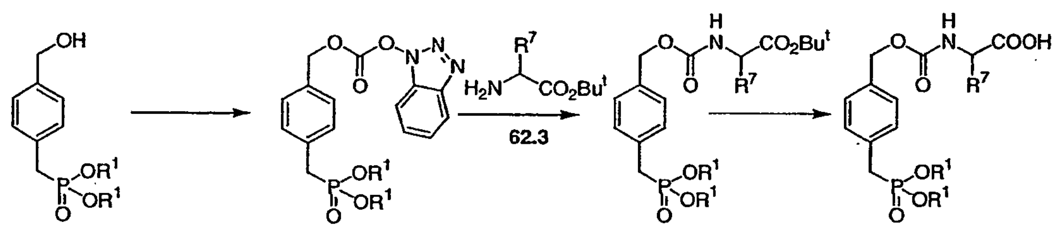
62.1 62.2 62.4 62.5

Example 1



62.6 62.7 62.8 62.9

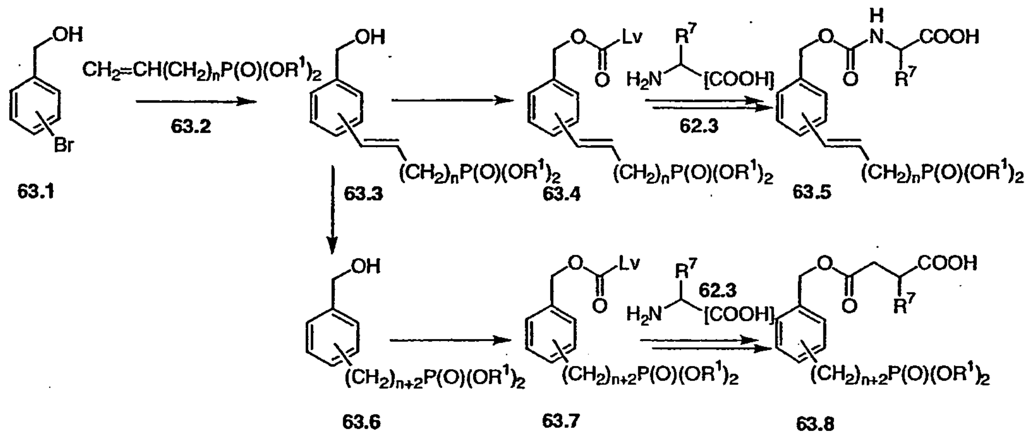
Example 2



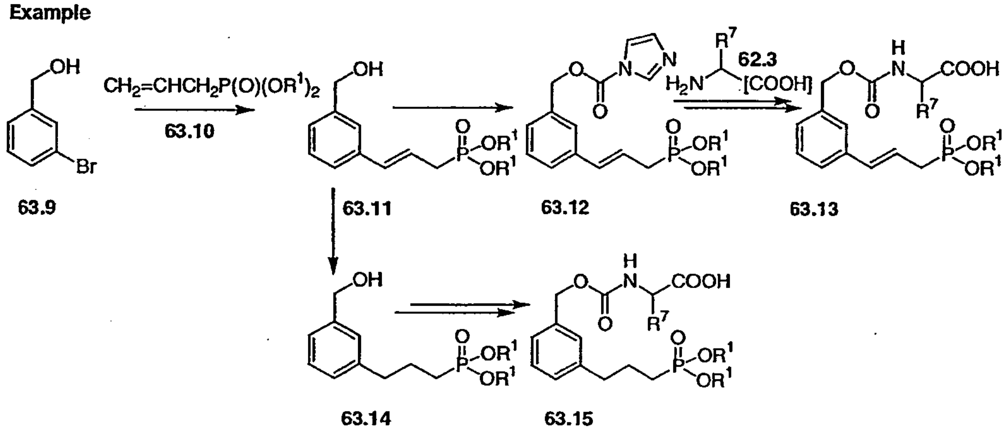
62.10 62.11 61.12 61.13

Scheme 63

Method

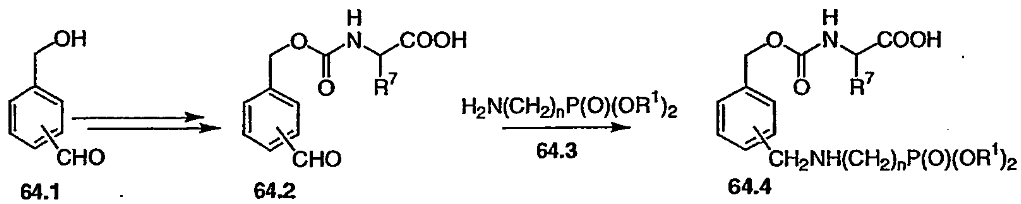


Example

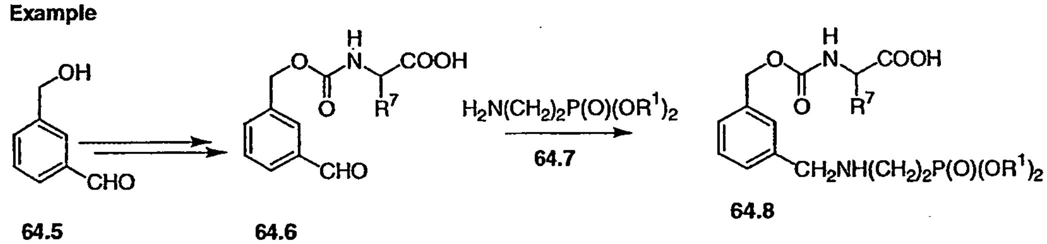


Scheme 64

Method

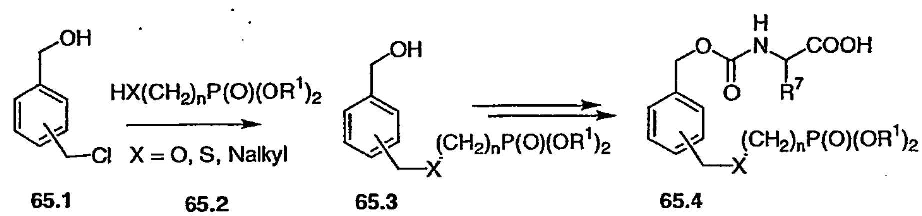


Example

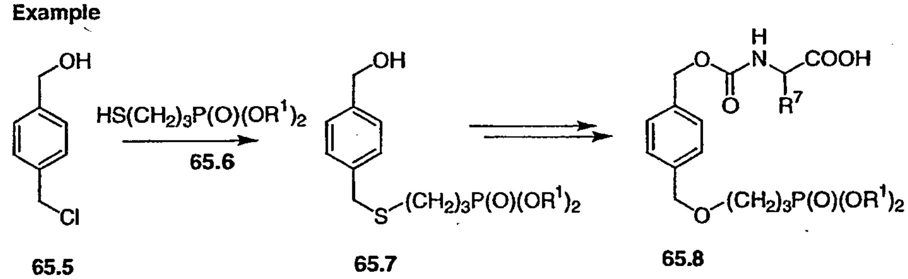


Scheme 65

Method



Example



Preparation of pyridinyloxymethyl piperidine derivatives incorporating phosphonate groups.

Scheme **66** illustrates the preparation of phosphonate-containing analogs of the amine **A12** in which the phosphonate moiety is attached to the pyridine ring by means of a heteroatom and an alkylene chain. In this procedure, 2-bromo-4-hydroxymethylpyridine, the preparation of which is described in Chem. Pharm. Bull., 1990, 38, 2446, is subjected to a nucleophilic

displacement reaction with a dialkyl hydroxy, thio or aminoalkyl-substituted alkyl phosphonate **66.2**. The preparation of pyridine ethers, thioethers and amines by means of displacement reactions of 2-bromopyridines by alcohols, thiols and amines is described, for example, in Heterocyclic Compounds, Volume 3, R. A. Abramovitch, ed., Wiley, 1975, p. 597, 191, and 41 respectively. Equimolar amounts of the reactants are combined in a polar solvent such as dimethylformamide at ca 100°C in the presence of a base such as potassium carbonate. The displacement product **66.3** is then converted into the activated derivative **66.4**, in which Lv is a leaving group such as halo, methanesulfonyloxy, p-toluenesulfonyloxy and the like. The conversion of alcohols into chlorides and bromides is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 354ff and p. 356ff. For example, benzyl alcohols can be transformed into the chloro compounds, in which Ha is chloro, by reaction with triphenylphosphine and N-chlorosuccinimide, as described in J. Am. Chem. Soc., 106, 3286, 1984. Benzyl alcohols can be transformed into bromo compounds by reaction with carbon tetrabromide and triphenylphosphine, as described in J. Am. Chem. Soc., 92, 2139, 1970. Alcohols can be converted into sulfonate esters by treatment with the alkyl or aryl sulfonyl chloride and a base, in a solvent such as dichloromethane or pyridine. Preferably, the carbinol **66.3** is converted into the corresponding chloro compound, **66.4**, in which Lv is Cl, as described above. The product is then reacted with the piperidinol derivative **66.5**. The preparation of the compounds **66.5** is described in U.S. 5,614,533, and in J. Org. Chem., 1997, 62, 3440. The piperidinol derivative **66.5** is treated in dimethylformamide with a strong base such as sodium hydride, and the alkylating agent **66.4** is then added. The reaction proceeds to afford the ether product **66.6**, and the BOC protecting group is then removed to yield the free amine compound **66.7**. The removal of BOC protecting groups is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 328. The deprotection can be effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride or trifluoroacetic acid, or by reaction with trimethylsilyl iodide or aluminum chloride. Preferably, the BOC group is removed by treatment of the substrate **66.6** with hydrochloric acid, as described in J. Org. Chem., 1997, 62, 3440.

For example, 2-bromo-4-hydroxymethylpyridine **66.1** the preparation of which is described in Chem. Pharm. Bull., 1990, 38, 2446, is reacted in dimethylformamide solution at ca 80°C with an equimolar amount of a dialkyl mercaptoethyl phosphonate **66.8**, prepared as described in

Zh. Obschei. Khim., 1973, 43, 2364, and potassium carbonate, to yield the thioether product **66.9**. The product is then reacted with one molar equivalent of methanesulfonyl chloride in pyridine at 0°C, to produce the mesylate compound **66.10**. This material is reacted with the piperidinol reagent **66.5**, using the conditions described above, to afford the ether **66.11**. The BOC protecting group is then removed as previously described, to afford the amine product **66.12**.

Using the above procedures, but employing, in place of the mercaptoethyl phosphonate **66.8**, different hydroxy, mercapto or alkylamino phosphonates **66.2**, the corresponding products **66.7** are obtained.

Scheme **67** illustrates the preparation of phosphonate-containing analogs of the amine **A12** in which the phosphonate moiety is directly attached to the pyridine ring. In this procedure, a bromo-substituted 4-hydroxymethylpyridine **67.1** is coupled, in the presence of a palladium catalyst, with a dialkyl phosphite **67.2**. The reaction between aryl bromides and dialkyl phosphites to yield aryl phosphonates is described in Synthesis, 56, 1981, and in J. Med. Chem., 1992, 35, 1371. The reaction is conducted in an inert solvent such as toluene or xylene, at about 100°C, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium and a tertiary organic base such as triethylamine. The thus-obtained pyridylphosphonate **67.3** is then converted, as described above (Scheme **66**) into an activated derivative **67.4**, and the latter compound is transformed as described above into the amine **67.5**.

For example, 3-bromo-4-hydroxymethylpyridine **67.5**, prepared as described in Bioorg. Med. Chem. Lett., 1992, 2, 1619, is reacted with a dialkyl phosphite **67.2**, as described above, to prepare the phosphonate **67.7**. The product is then transformed into the chloro derivative by reaction with triphenylphosphine and N-chlorosuccinimide, and the product is converted, as described above (Scheme **66**) into the amine **67.9**.

Using the above procedures, but employing, in place of the 3-bromopyridine derivative **67.6**, different bromopyridines **67.1**, and/or different phosphites, the corresponding products **67.5** are obtained.

Scheme **68** illustrates the preparation of phosphonate-containing analogs of the amine **A12** in which the phosphonate moiety is attached to the pyridine ring by means of an amine group and

an alkyl chain. In this procedure, an amino-substituted 4-hydroxymethylpyridine **68.1** is subjected to a reductive amination reaction with a dialkyl formylalkyl phosphonate **68.2**. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in J. Org. Chem., 55, 2552, 1990. The amine product **68.3** is then converted, as described above, into the piperidine derivative **68.5**.

For example, 2-amino-4-hydroymethylpyridine **68.6**, prepared as described in Aust. J. Chem., 1993, 46, 9897, is reacted in ethanol solution with a dialkyl formylmethylphosphonate **68.7**, prepared as described in Zh. Obschei. Khim., 1987, 57, 2793, in the presence of sodium cyanoborohydride, to yield the amine product **68.8**. This material is then transformed into the chloro derivative **68.9** by reaction with hydrogen chloride in ether. The chloro product is then transformed, as described above, into the piperidine derivative **68.10**.

Using the above procedures, but employing, in place of the 2-aminopyridine derivative **68.6**, different aminopyridines **68.1**, and/or different formylalkyl phosphonates **68.2** the corresponding products **68.5** are obtained.

Scheme **69** illustrates the preparation of phosphonate-containing analogs of the amine **A12** in which the phosphonate moiety is attached to the pyridine ring by means of a saturated or unsaturated alkyl chain. In this procedure, a bromo-substituted 4-hydroxymethylpyridine **69.1** is coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenyl phosphonate **69.2**. The coupling of aryl bromides and olefins is described above (Scheme **26**). The product is then converted, as described above, into the piperidine derivative **69.5**. Optionally, the latter compound can be reduced, for example as described above in Scheme **26**, to afford the saturated analog **69.6**.

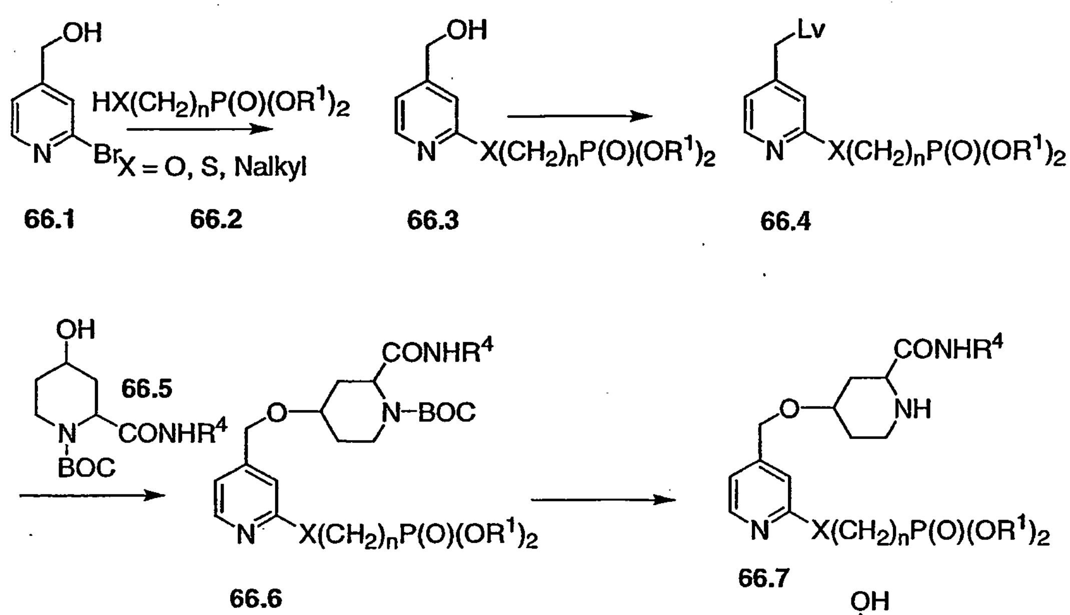
For example, 3-bromo-4-hydroxymethylpyridine **69.7**, prepared as described in Bioorg. Med. Chem. Lett., 1992, 2, 1619, is coupled with a dialkyl vinylphosphonate **69.8**, prepared as described in Synthesis, 1983, 556, to yield the olefinic product **69.9**. The product is reacted

with one molar equivalent of p-toluenesulfonyl chloride in pyridine at ambient temperature to afford the tosylate **69.10**. The latter compound is then transformed, as previously described, into the piperidine derivative **69.11**. Optionally, the latter compound is reduced, for example by reaction with diimide, to yield the saturated analog **69.12**.

Using the above procedures, but employing, in place of the 3-bromopyridine derivative **69.7**, different bromopyridines **69.1**, and/or different alkenyl phosphonates **69.2** the corresponding products **69.5** and **69.6** are obtained.

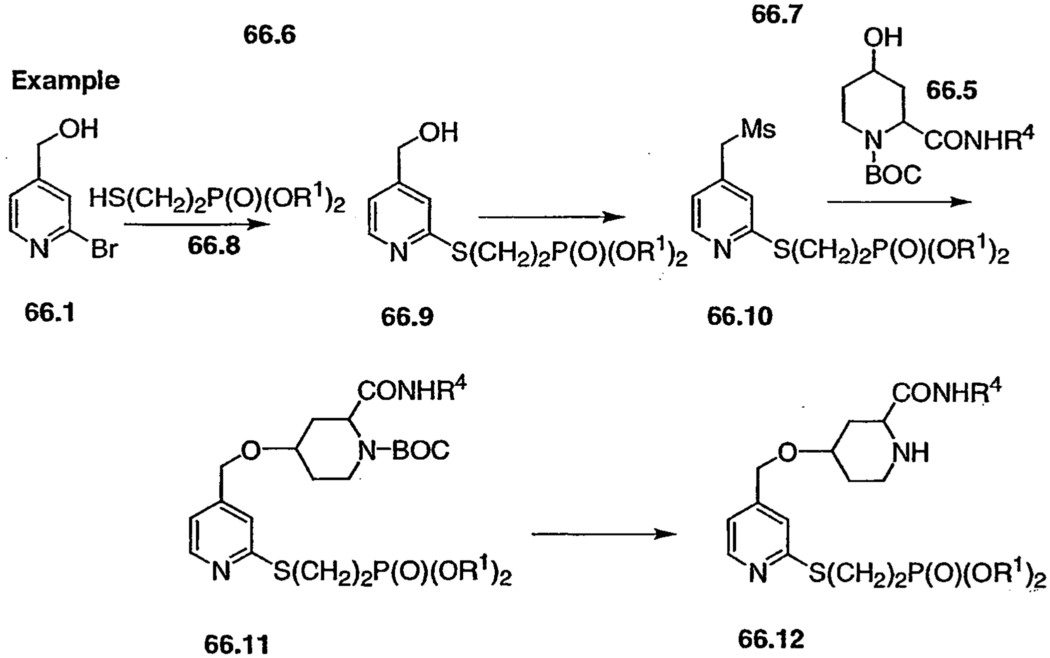
Scheme 66

Method



66.1 66.2 66.3 66.4 66.5 66.6 66.7

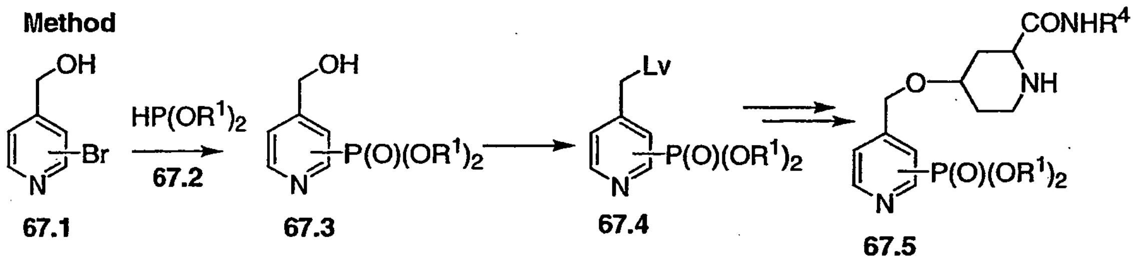
Example



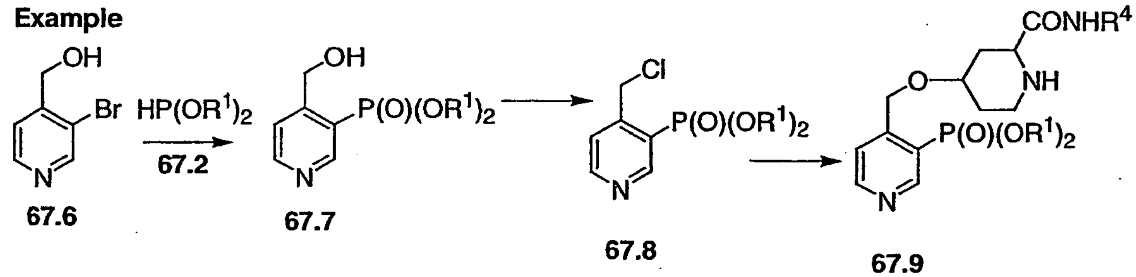
66.1 66.8 66.9 66.10 66.5 66.11 66.12

Scheme 67

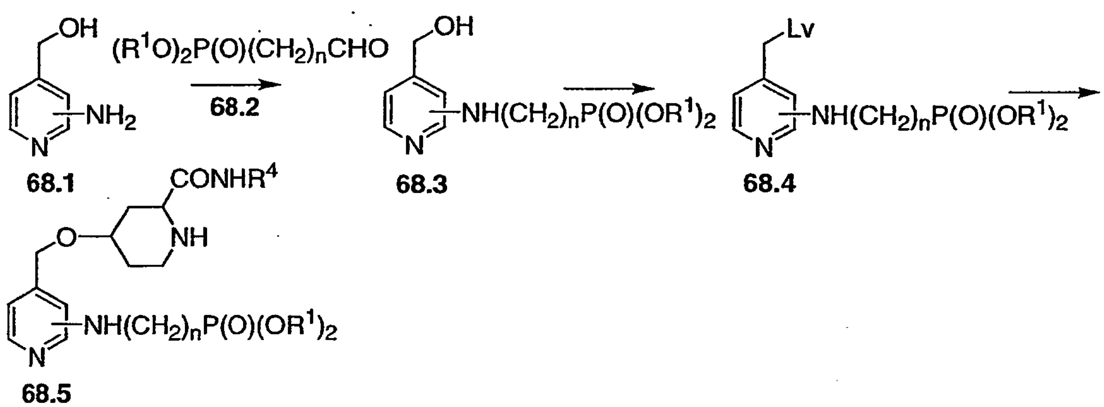
Method



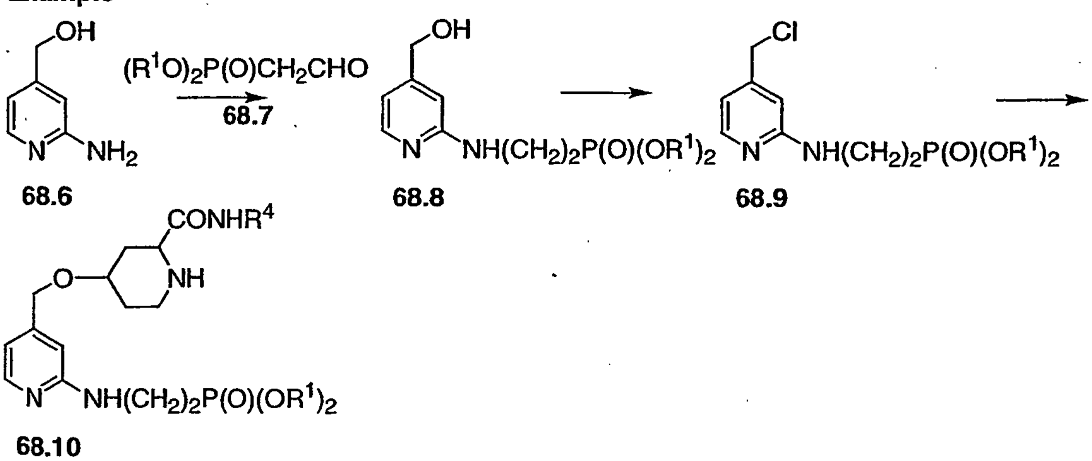
Example



Scheme 68
Method

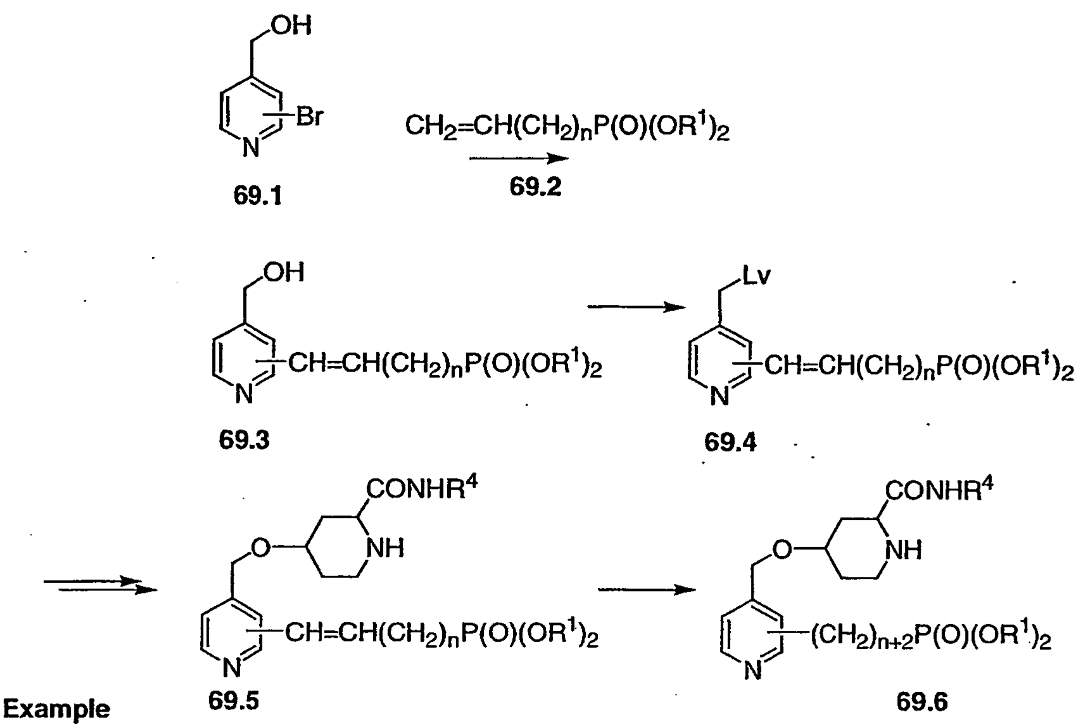


Example

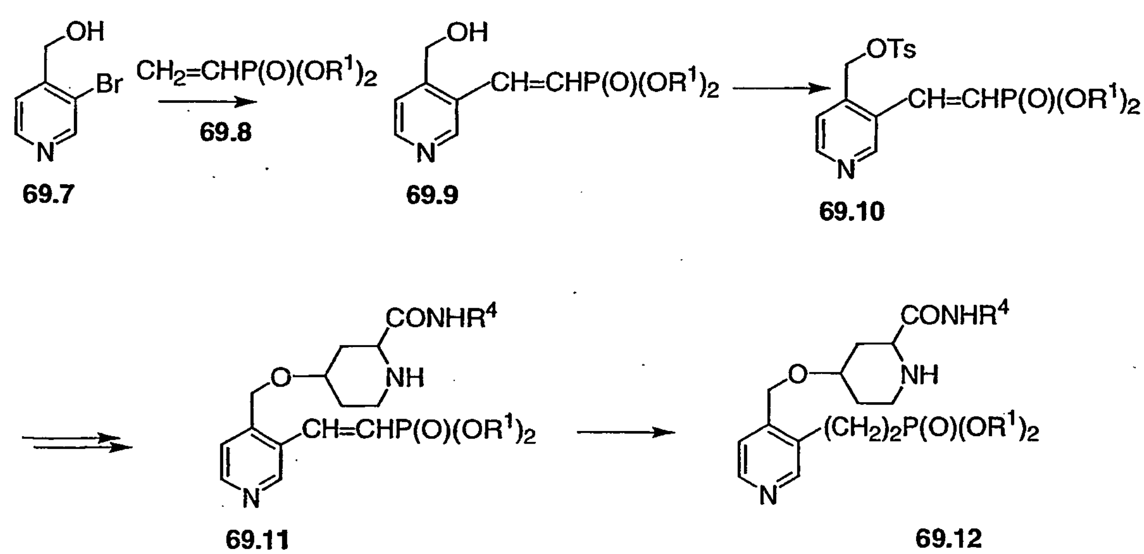


Scheme 69

Method



Example



General applicability of methods for introduction of phosphonate substituents.

The procedures described herein for the introduction of phosphonate moieties are, with appropriate modifications, transferable to different chemical substrates. For example, the methods described above for the introduction of phosphonate groups into the quinoline-2-carboxylic moiety (Schemes **24-27**), can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate groups into the phenylalanine, thiophenol, tert-butylamine and decahydroisoquinoline moieties. Similarly, the methods described above for the introduction of phosphonate groups into the phenylalanine moiety (Schemes **28-34**), the thiophenol moiety (Schemes **35-44**) the tert-butylamine moiety (Schemes **45-48**), decahydroisoquinoline moiety (Schemes **48a-52**), dimethylphenoxyacetic acids (Schemes **56 - 61**), benzyl carbamates (Schemes **62 - 65**) and pyridines (Schemes **66 - 69**) can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate groups into the quinoline-2-carboxylic acid component.

Preparation of (Pyridin-3-yloxy)-acetic acids incorporating phosphonate moieties.

Scheme **70** illustrates two alternative methods by means of which (pyridin-3-yloxy)-acetic acids bearing phosphonate moieties may be prepared. The phosphonate group may be introduced into the pyridyl moiety, followed by attachment of the acetic acid group, or the phosphonate group may be introduced into a preformed (Pyridin-3-yloxy)-acetic acid intermediate. In the first sequence, a substituted 3-hydroxypyridine **70.1**, in which the substituent B is a precursor to the group link-$P(O)(OR^1)_2$, and in which the aryl hydroxyl may or may not be protected, depending on the reactions to be performed, is converted into a phosphonate-containing compound **70.2**. Methods for the conversion of the substituent B into the group link-$P(O)(OR^1)_2$ are described in Schemes **25 - 75**.

The protected aryl hydroxyl group present in the phosphonate-containing product **70.2** is then deprotected, using methods described below, to afford the phenol **70.3**.

The product **70.3** is then transformed into the corresponding (pyridin-3-yloxy) acetic acid **70.4**, in a two step procedure. In the first step, the phenol **70.3** is reacted with an ester of bromoacetic acid **70.9**, in which R is an alkyl group or a protecting group. Methods for the protection of carboxylic acids are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff. The alkylation of aryl

hydroxyl groups to afford aryl ethers is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 446ff. Typically, the aryl reagent and the alkylating agent are reacted together in the presence of an organic or inorganic base, such as, for example, diazabicyclononene, (DBN) or potassium carbonate, in a polar organic solvent such as, for example, dimethylformamide or acetonitrile.

Preferably, equimolar amounts of the phenol **70.3** and ethyl bromoacetate are reacted together in the presence of cesium carbonate, in dioxan at reflux temperature, for example as described in U.S. Patent 5,914,332, to afford the ester **70.4**.

The thus-obtained ester **70.4** is then hydrolyzed to afford the carboxylic acid **70.5**. The methods used for this reaction depend on the nature of the group R. If R is an alkyl group such as methyl, hydrolysis can be effected by treatment of the ester with aqueous or aqueous alcoholic base, or by use of an esterase enzyme such as porcine liver esterase. If R is a protecting group, methods for hydrolysis are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff.

Preferably, the ester product **70.4** which R is ethyl is hydrolyzed to the carboxylic acid **70.5** by reaction with lithium hydroxide in aqueous methanol at ambient temperature, as described in U.S. Patent 5,914,332.

Alternatively, an appropriately substituted 3-hydroxypyridine **70.6**, in which the substituent B is a precursor to the group link-$P(O)(OR^1)_2$, is transformed into the corresponding acetic acid ester **70.7**. The conditions employed for the alkylation reaction are similar to those described above for the conversion of the phenol **70.3** into the ester **70.4**.

The acetic acid ester **70.7** is then converted into the carboxylic acid **70.5** using the 2 step procedure shown above, involving transformation of the group B into the group link-$P(O)(OR^1)_2$ followed by ester hydrolysis of the acetic acid ester. The group B which is present in the ester **70.7** may be transformed into the group link-$P(O)(OR^1)_2$ either before or after hydrolysis of the ester moiety into the carboxylic acid group, depending on the nature of the chemical transformations required.

Schemes **70-75** illustrate the preparation of (Pyridin-3-yloxy)-acetic acids incorporating phosphonate ester groups. The procedures shown can also be applied to the preparation of acetic esters acids **70.7**, with, if appropriate, modifications made according to the knowledge of one skilled in the art.

Scheme **71** depicts the preparation of (pyridin-3-yloxy) acetic acids incorporating a phosphonate group linked to the pyridyl ring by means of a saturated or unsaturated alkylene chain. In this procedure, an optionally protected halo-substituted 3-hydroxypyridine **71.1** is coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenyl phosphonate **71.2**. The coupling of aryl bromides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503. The aryl halide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) or palladium (2) catalyst. Following the coupling reaction, the product **71.3** is converted, using the procedures described above, (Scheme **70**) into the corresponding (pyridin-3-yloxy) acetic acid **71.4**. Alternatively, the olefinic product **71.3** is reduced to afford the saturated derivative **71.5**. Methods for the reduction of carbon-carbon double bonds are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 6. The methods include catalytic reduction, or chemical reduction employing, for example, diborane or diimide. Following the reduction reaction, the product **71.5** is converted, as described above, (Scheme **70**) into the corresponding (pyridin-3-yloxy) acetic acid **71.6**.

For example, 2-iodo-5-hydroxy pyridine **71.7**, prepared as described in J. Org. Chem., 1990, 55, 18, p. 5287, is converted into the tert-butyldimethylsilyl ether **71.8**, by reaction with chloro-tert-butyldimethylsilane, and a base such as imidazole, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990 p. 77. The product **71.8** is reacted with an equimolar amount of a dialkyl allyl phosphonate **71.9**, for example diethyl allylphosphonate (Aldrich) in the presence of ca. 3 mol % of bis(triphenylphosphine) palladium(II) chloride, in dimethylformamide at ca. 60°C, to produce the coupled product **71.10**. Alternatively see J. Med. Chem. 1999, 42, 4, p. 669 for alternative conditions for this reaction. The silyl group is removed, for example by the treatment of the ether **71.10** with a solution of tetrabutylammonium fluoride in tetrahydrofuran, as described in J. Am. Chem., Soc., 94, 6190, 1972, to afford the phenol **71.11**. This compound is converted, employing the procedures described above, (Scheme **70**) into the corresponding (pyridin-3-yloxy) acetic acid **71.12**. Alternatively, the unsaturated compound **71.11** is reduced, for example by catalytic hydrogenation employing 5% palladium on carbon as catalyst, in an alcoholic solvent such as methanol, as described, for example, in Hydrogenation Methods, by R. N. Rylander, Academic Press, 1985, Ch. 2, to afford the saturated analog **71.13**. This

compound is converted, employing the procedures described above, (Scheme **70**) into the corresponding (pyridin-3-yloxy) acetic acid **71.14**.

Using the above procedures, but employing, in place of 2-iodo-5-hydroxy pyridine **71.7**, different iodo or bromohydroxypyridines **71.1**, and/or different dialkyl alkenyl phosphonates **71.2**, the corresponding products **71.4** and **71.6** are obtained.

In this and succeeding examples, the nature of the phosphonate ester group can be varied, either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described above (Scheme **54**).

Scheme **72** illustrates the preparation of phosphonate-containing analogs of (pyridin-3-yloxy) acetic acids in which the phosphonate moiety is attached to the pyridine ring by means of a heteroatom and an alkyl chain. In this procedure, a suitably protected 2-halo-5-hydroxypyridine, (see Scheme **71**) is subjected to a nucleophilic displacement reaction with a dialkyl hydroxy, thio or aminoalkyl-substituted alkyl phosphonate **72.2**. The preparation of pyridine ethers, thioethers and amines by means of displacement reactions of 2-bromopyridines, by alcohols, thiols and amines is described, for example, in Heterocyclic Compounds, Volume 3, R. A. Abramovitch, ed., Wiley, 1975, p. 597, 191, and 41 respectively. Equimolar amounts of the reactants are combined in a polar solvent such as dimethylformamide at ca 100°C in the presence of a base such as potassium carbonate. The displacement product **72.3** is then converted into the hydroxyl derivative **72.4** and then into the (pyridin-3-yloxy) acetic acid phosphonate ester **72.5** using the procedures described above (Scheme **70**).

For example, 2-iodo-5-hydroxypyridine **71.7** (Scheme **71**) is treated with benzyl bromide in the presence of base such as potassium carbonate as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999, p. 266 to give **72.6**. The benzyl ether **72.6** is reacted in dimethylformamide solution at ca 80°C with an equimolar amount of a dialkyl mercaptoethyl phosphonate **72.7**, prepared as described in Zh. Obschei. Khim., 1973, 43, 2364, and potassium carbonate, to yield the thioether product **72.8**. The benzyl group is then removed by catalytic hydrogenation employing 5% palladium on carbon as catalyst, in an alcoholic solvent such as methanol, as described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p.

266ff., to afford the hydroxyl compound **72.9**. The product **72.9** is then converted into the (pyridin-3-yloxy) acetic acid phosphonate ester **72.10** using the procedures described above (Scheme **70**).

Using the above procedures, but employing, in place of the mercaptoethyl phosphonate **72.7**, different hydroxy, mercapto or alkylamino phosphonates **72.2**, and/or in place of the pyridine **71.7** different halo pyridines **71.1**, the corresponding products **72.5** are obtained.

Scheme **73** illustrates the preparation of phosphonate-containing analogs of (pyridin-3-yloxy) acetic acids in which the phosphonate moiety is directly attached to the pyridine ring. In this procedure, a suitably protected 2-bromo-5-hydroxypyridine **73.1** is coupled, in the presence of a palladium catalyst, with a dialkyl phosphite **73.2**. The reaction between aryl bromides and dialkyl phosphites to yield aryl phosphonates is described in Synthesis, **70**, 1981, and in J. Med. Chem., 1992, 35, 1371. The reaction is conducted in an inert solvent such as toluene or xylene, at about 100°C, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium and a tertiary organic base such as triethylamine. The thus-obtained pyridylphosphonate **73.3** is then converted, as described above (Scheme **72**) into the (pyridin-3-yloxy) acetic acid phosphonate ester **73.5**.

For example, 3-bromo-5-hydroxypyridine **73.6** (Synchem-OHG) is treated with benzyl bromide in the presence of base such as potassium carbonate as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999, p. 266 to give **73.7**. The product **73.7** is then treated with a dialkylphosphite **73.2** as described above to give the phosphonate **73.8**. Employing the conditions described above (Scheme **72**) **73.8** is converted in several steps to the (pyridin-3-yloxy) acetic acid phosphonate ester **73.10**.

Using the above procedures, but employing, in place of the 3-bromopyridine derivative **73.6**, different bromopyridines **73.1**, and/or different phosphites, the corresponding products **73.5** are obtained.

Scheme **74** illustrates the preparation of (pyridin-3-yloxy) acetic acids incorporating a phosphonate group attached to the pyridyl ring by means of a heteroatom and an alkylene chain. The compounds are obtained by means of alkylation reactions in which an hydroxy, thio or amino-substituted 3-hydroxy pyridine **74.1**, protected at the 3-hydroxyl position is reacted, in the presence of a base such as, for example, potassium carbonate, and optionally in

the presence of a catalytic amount of an iodide such as potassium iodide, with a dialkyl bromoalkyl phosphonate **74.6**. The reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile at from ambient temperature to about 80°C. The product of the alkylation reaction, **74.2** is then converted, as described above for converting **72.3** to **72.5** (Scheme **72**) into the acid **74.5**.

Alternatively, the protected pyridine **74.7** is converted to the acetic acid ester derivative **74.8** using the procedures described above in Scheme **70**. The acetic acid ester **74.8**, is then deprotected following the procedures described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999, ch 3,6, and 7, and the product treated with a dialkyl bromoalkyl phosphonate **74.6** to give **74.4**. The ester **74.4** is converted to the acid **74.5** using the procedures described above (Scheme **70**).

For example, 3-benzyloxy, 5-hydroxy pyridine **74.10**, prepared as described Bioorg and Med. Chem. Lett. 1998, p. 2797, is converted to the ester **74.11** by treatment with ethylbromoacetate as described above (Scheme **70**). The benzyl group is removed, for example by catalytic hydrogenation employing 5% palladium on carbon as catalyst, in an alcoholic solvent such as methanol, as described, for example, in Hydrogenation Methods, by R. N. Rylander, Academic Press, 1985, Ch. 2, to afford the hydroxy pyridine **74.12**. The product **74.12** is reacted in dimethylformamide at ca. 60°C with an equimolar amount of a dialkyl bromobutyl phosphonate **74.14**, the preparation of which is described in Synthesis, 1994, 9, 909, in the presence of ca. 5 molar equivalents of potassium carbonate, to afford the phosphonate ether product **74.13**. This compound is converted, employing the procedures described above, (Scheme **70**) into the corresponding acid **74.15**.

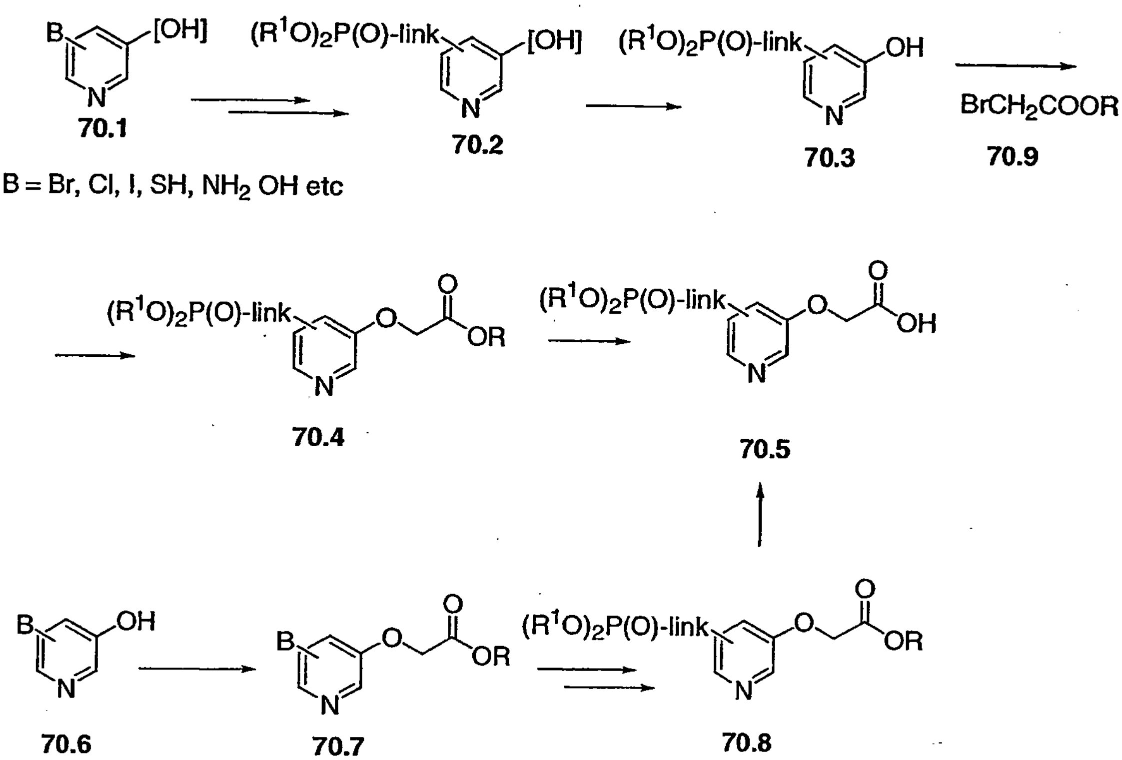
Using the above procedures, but employing, in place of the pyridine **74.10**, different hydroxy, thio or aminophenols **74.1**, and/or different dialkyl bromoalkyl phosphonates **74.6**, the corresponding products **74.5** are obtained.

Scheme **75** illustrates the preparation of (Pyridin-3-yloxy)-acetic acids incorporating a phosphonate ester which is attached to the pyridyl group by means of a carbon chain incorporating a nitrogen atom. The compounds **75.4** are obtained by means of a reductive alkylation reaction between hydroxyl protected 3-hydroxypyridyl aldehyde **75.1** and an aminoalkyl phosphonate ester **75.2**. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations,

by R. C. Larock, VCH, p. 421. In this procedure, the amine component **75.2** and the aldehyde component **75.1** are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride or diisobutylaluminum hydride, to yield the amine product **75.3**. The amination product **75.3** is then deprotected according to procedures described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999, ch3, and subsequently converted into the (pyridin-3-yloxy) acetic acid compound **75.4**, using the alkylation and ester hydrolysis procedures described above (Scheme **70**).

For example, the ester **75.5** (TCI-US) is reacted with benzyl bromide in the presence of base such as potassium carbonate as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999, p. 266 to give **75.6**. The benzyl ether **75.6** is then converted to the aldehyde **75.7** by reaction with DIBAL (see Comprehensive Organic Transformations, by R. C. Larock, 2nd Edition, 1999, p. 1267. for examples). Equimolar amounts of aldehyde **75.7,** and a dialkyl aminoethyl phosphonate **75.8**, the preparation of which is described in J. Org. Chem., 2000, 65, 676, are reacted together in the presence of sodium cyanoborohydride and acetic acid, as described, for example, in J. Amer. Chem. Soc., 91, 3996, 1969, to afford the amine product **75.9**. The benzyl group is then removed by catalytic hydrogenation employing 5% palladium on carbon as catalyst, in an alcoholic solvent such as methanol, as described, for example, in Hydrogenation Methods, by R. N. Rylander, Academic Press, 1985, Ch. 2, to afford the hydroxyl compound **75.10**. The product **75.10** is then converted into the acetic acid **75.11**, as described above (Scheme **70**). Using the above procedures, but employing, in place of the aldehyde **75.7**, different aldehydes **75.1**, and/or different aminoalkyl phosphonates **75.2**, the corresponding products **75.4** are obtained.

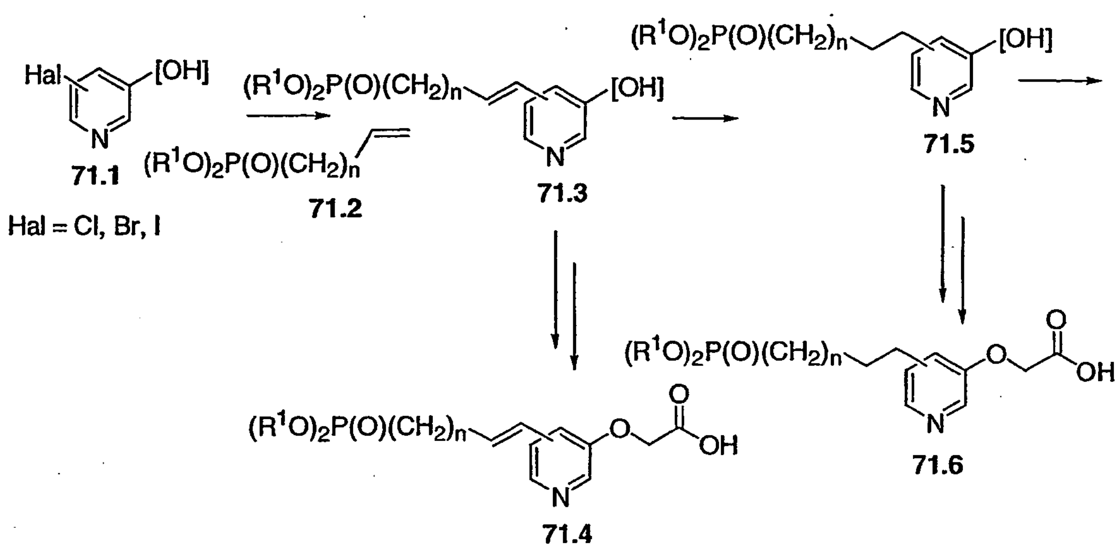
Scheme 70



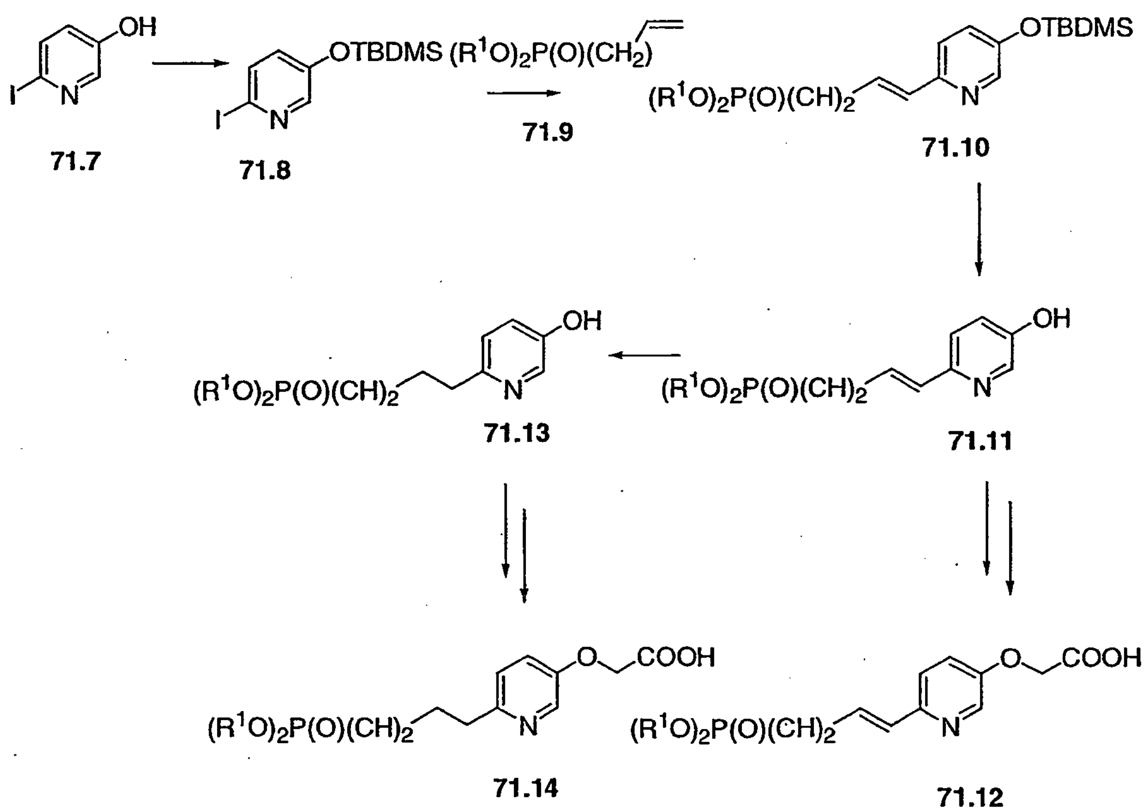
B = Br, Cl, I, SH, NH_2 OH etc

B = Br, Cl, I, [SH], [NH_2], [OH] etc

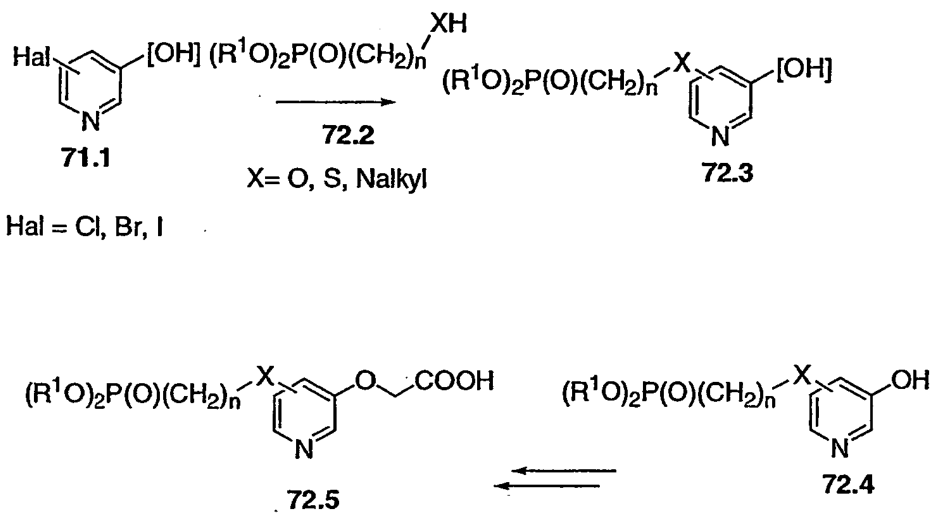
Scheme 71



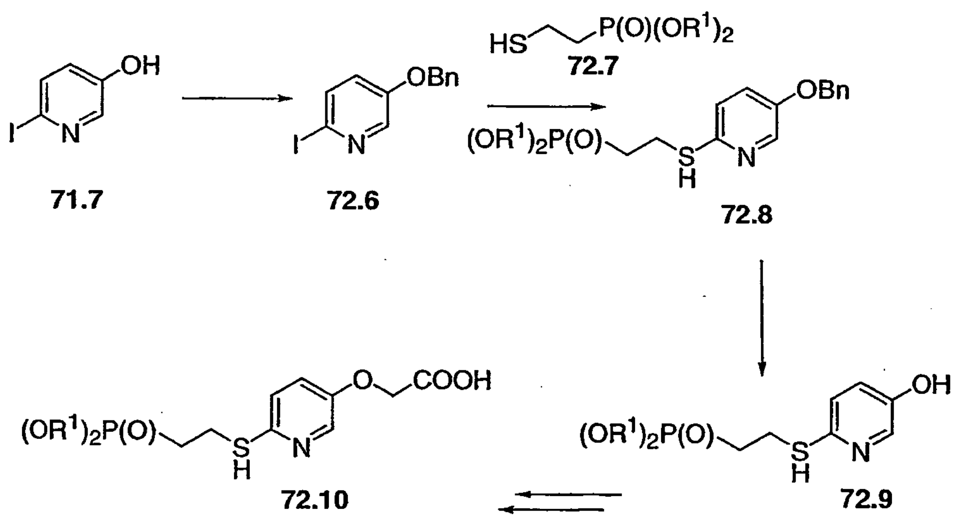
Example



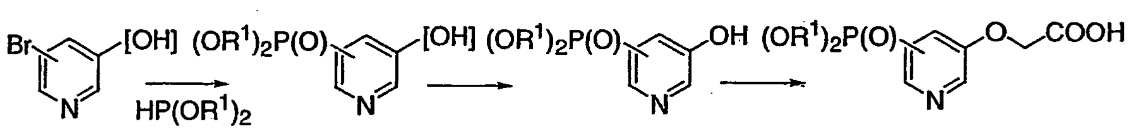
Scheme 72



Example

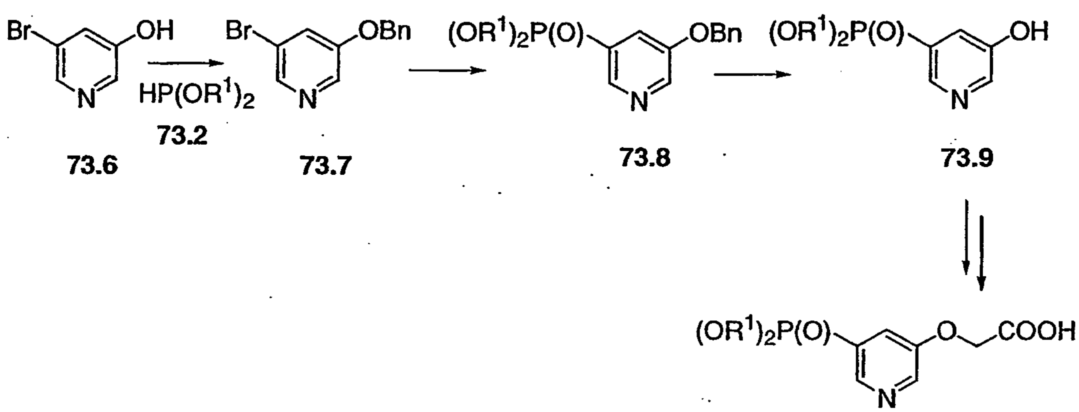


Scheme 73



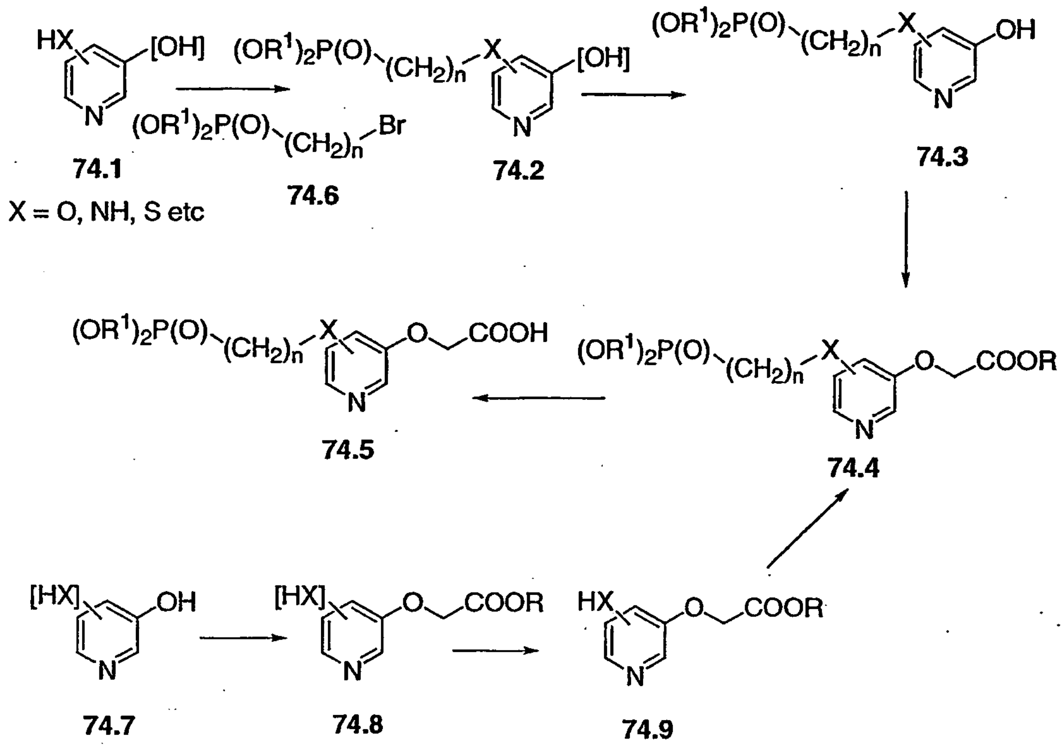
73.1 73.2 73.3 73.4 73.5

Example

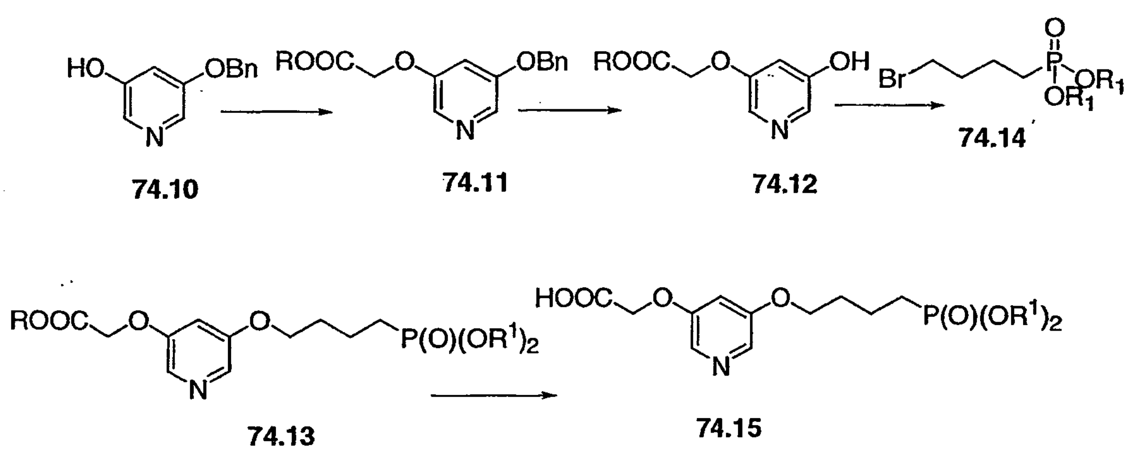


73.6 73.2 73.7 73.8 73.9 73.10

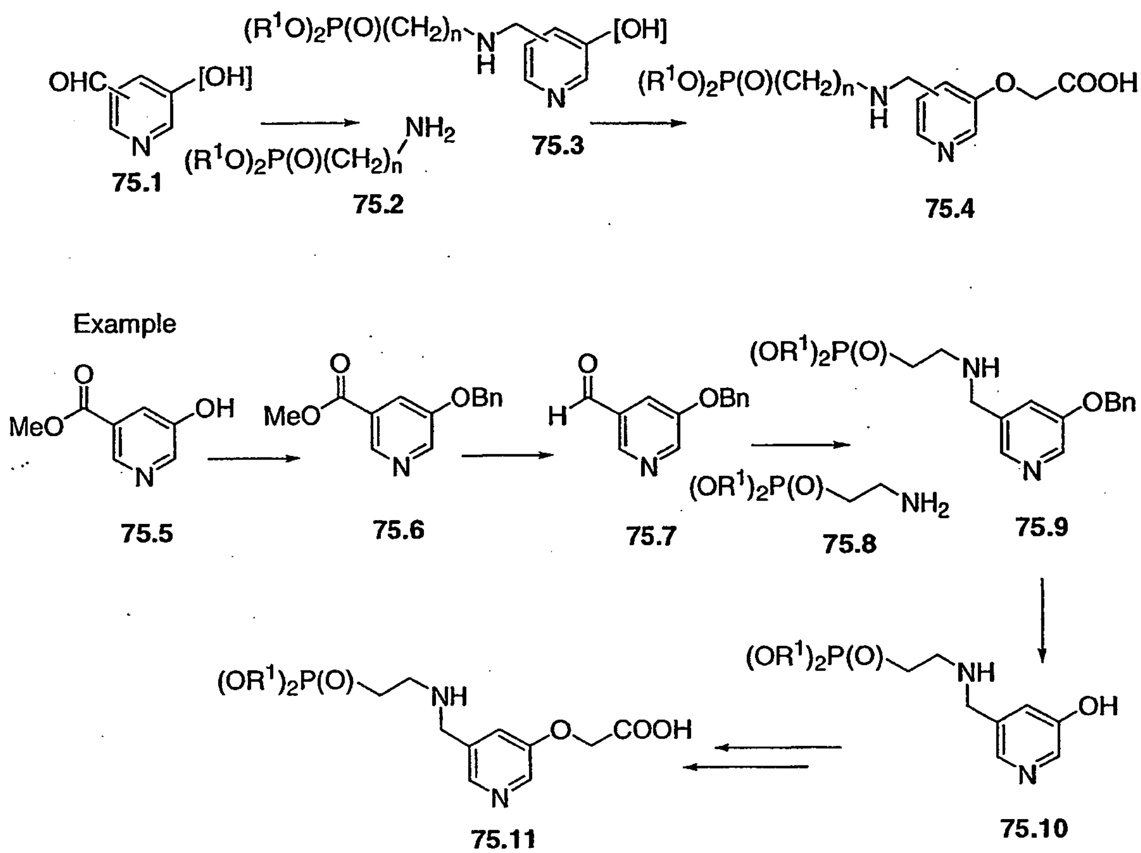
Scheme 74



Example



Scheme 75



Ritonavir-like phosphonate protease inhibitors (RLPPI)

Chemistry for Ritonavir analogs.

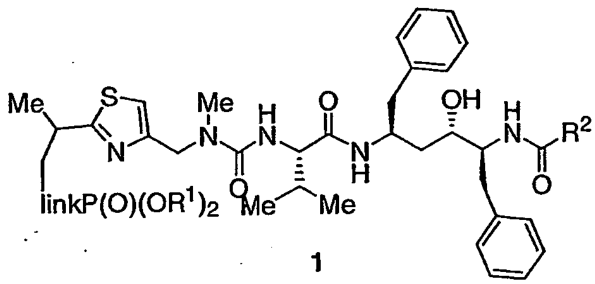
Preparation of the intermediate phosphonate esters.

The structures of the intermediate phosphonate esters **1 to 7**, and the structures for the component groups R^1 of this invention are shown in Chart 1. The structures of the components R^2COOH, R^3COOH and R^4 are shown in Charts **2a, 2b** and **2c**. Specific stereoisomers of some of the structures are shown in Charts 1 and 2; however, all stereoisomers are utilized in the syntheses of the compounds **1** to **7**. Subsequent chemical modifications to the compounds **1** to **7**, as described herein, permit the synthesis of the final compounds of this invention.

The intermediate compounds **1** to **7** incorporate a phosphonate moiety connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures. Charts **3** and **4** illustrate examples of the linking groups present in the structures **1** – **7**, and in which "etc" refers to the scaffold, e.g., ritonavir.

Schemes **1** - **28** illustrate the syntheses of the intermediate phosphonate compounds of this invention, **1**- **5**, and of the intermediate compounds necessary for their synthesis. The preparation of the compounds **6** and **7**, in which the phosphonate moiety is attached to the R^2COOH or R^3COOH group, is also described below.

Chart 1 Structures of the intermediate phosphonate esters 1-7



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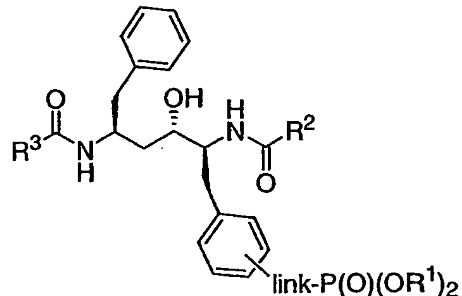

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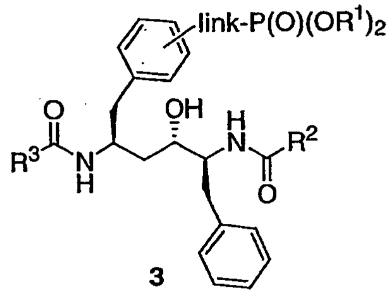

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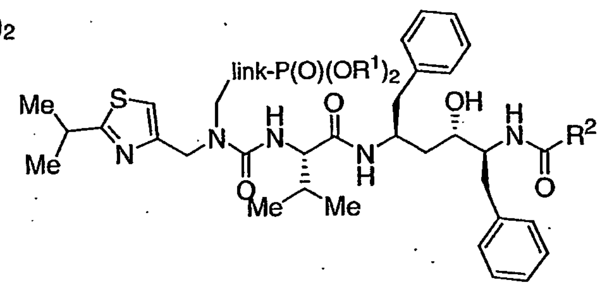

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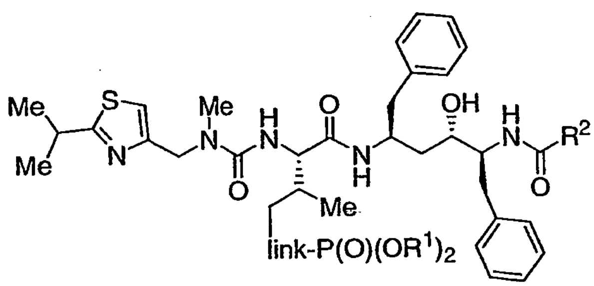

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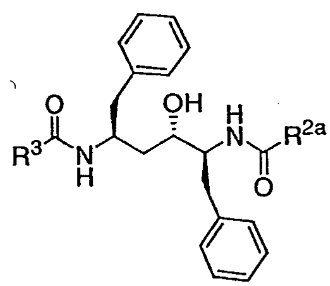

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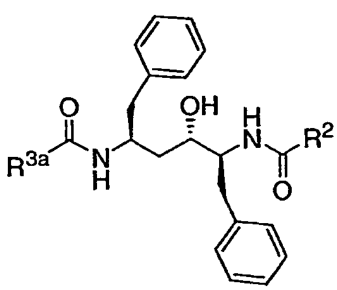
R^{2a} = phosphonate-containing R^2 group

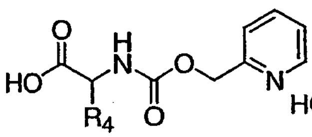


7

R^{3a} = phosphonate-containing R^3 group

R^1 = H, alkyl, alkenyl, aralkyl, aryl.

Chart 2a Structures of the R^2COOH and R^3COOH components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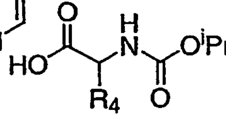
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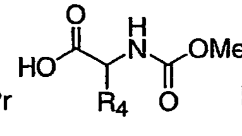
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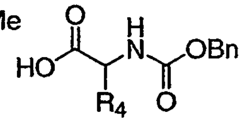
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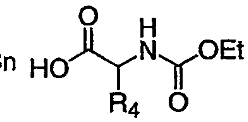
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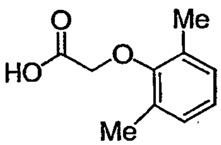
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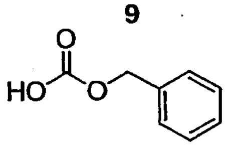
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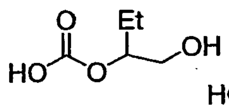
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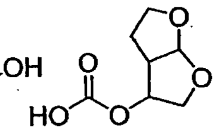
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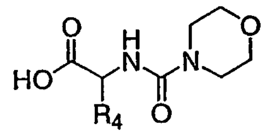
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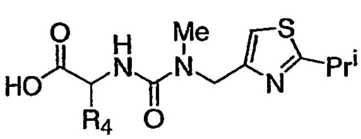
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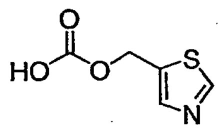
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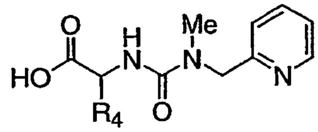
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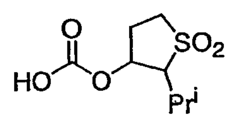
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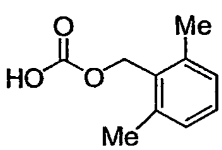
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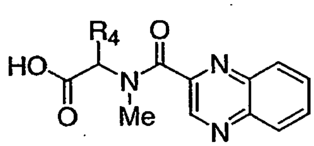
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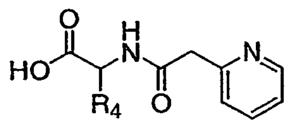
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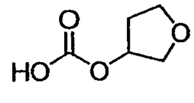
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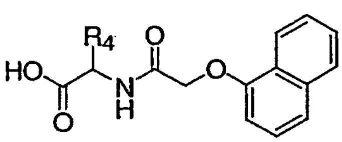
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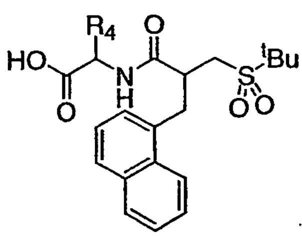
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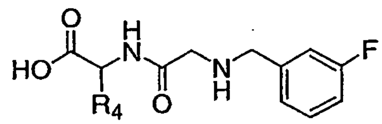
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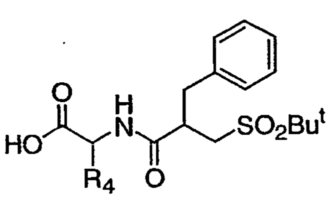
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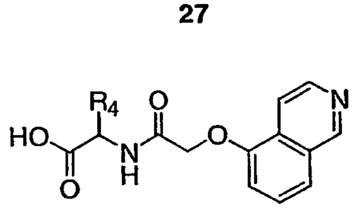
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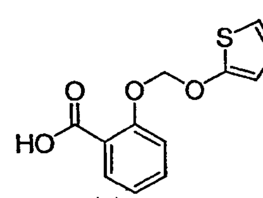
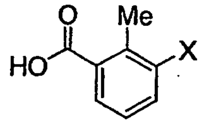
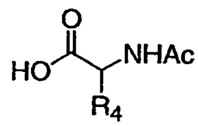

31

R^4 = alkyl, $CH_2SO_2CH_3$,$C(CH_3)_2SO_2CH_3$,CH_2CONH_2, CH_2SCH_3, imidaz-4-ylmethyl, CH_2NHAc, $CH_2NHCOCF_3$

Chart 2b Structures of the R^2COOH and R^3COOH components



32
X = OH, NH_2



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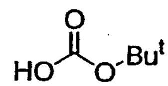

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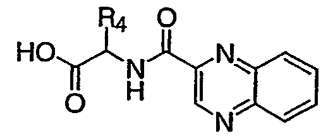

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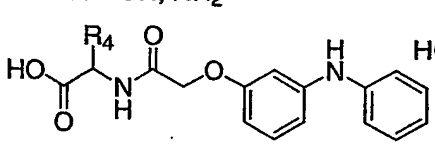

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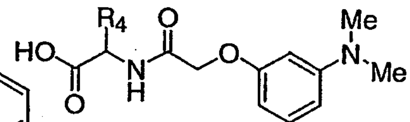

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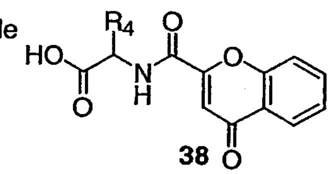

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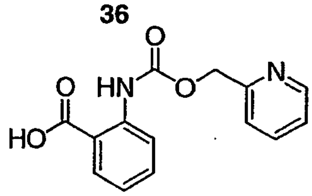

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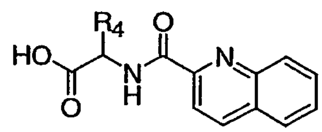

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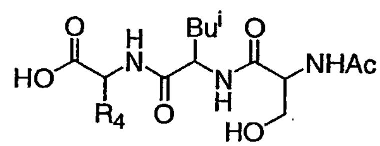

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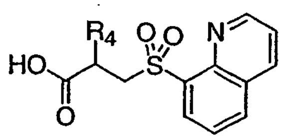

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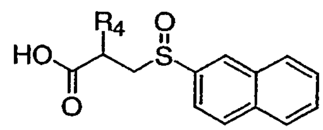

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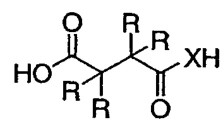
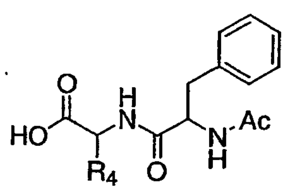


44
X = O, NH
R = H, alkyl



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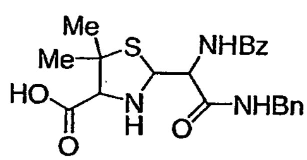

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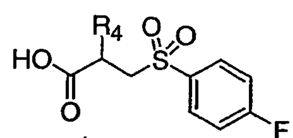

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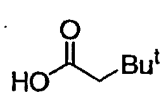

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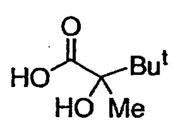

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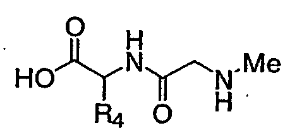
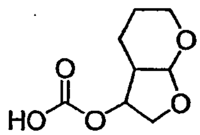


50

R^4 = alkyl, $CH_2SO_2CH_3$,$C(CH_3)_2SO_2CH_3$,CH_2CONH_2, CH_2SCH_3, imidaz-4-ylmethyl, CH_2NHAc, $CH_2NHCOCF_3$

Chart 2c Structures of the R^2COOH and R^3COOH components



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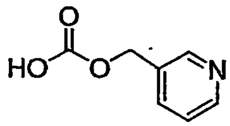

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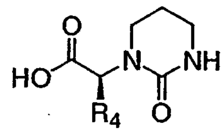

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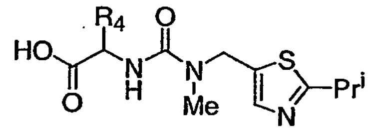


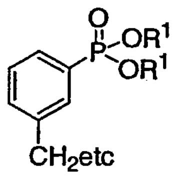
54

R^4 = alkyl, $CH_2SO_2CH_3$, $C(CH_3)_2SO_2CH_3$, CH_2CONH_2, CH_2SCH_3, imidaz-4-ylmethyl, CH_2NHAc, $CH_2NHCOCF_3$

Chart 3 Examples of the linking group between the scaffold and the phosphonate moiety.

link **examples**

direct bond



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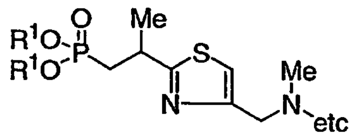

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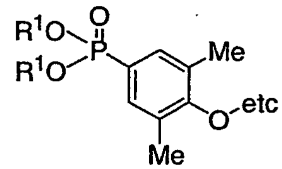

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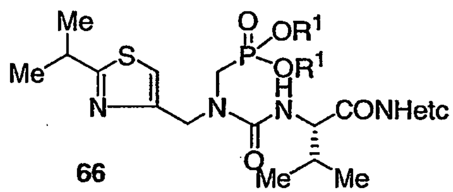

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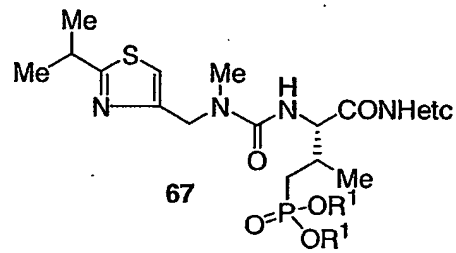
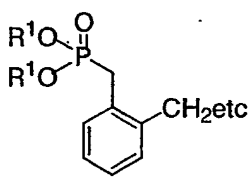


67

single carbon



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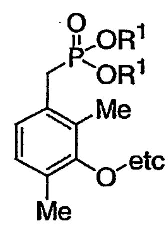

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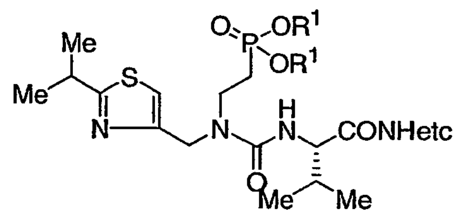

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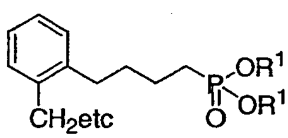
multiple carbon



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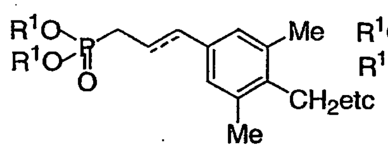

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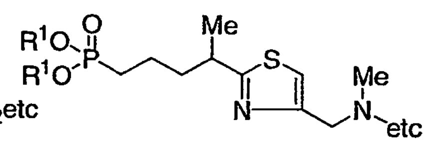
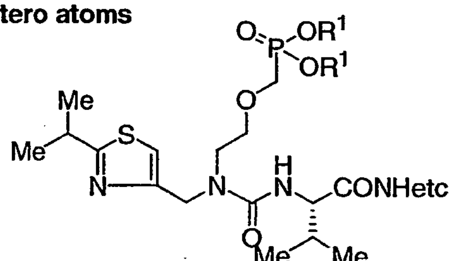


73

hetero atoms



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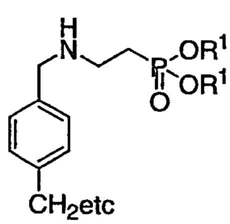

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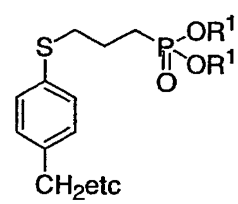
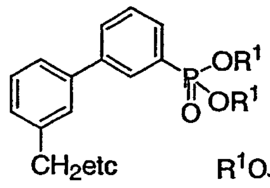


76

Chart 4 Examples of the linking group between the scaffold and the phosphonate moiety.

link | **examples**

aryl, heteroaryl



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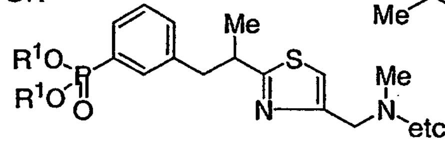

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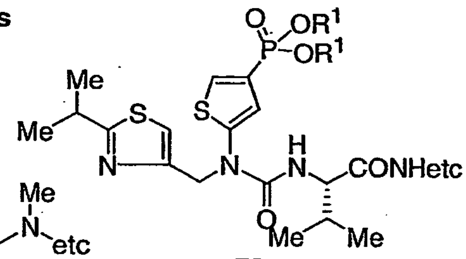
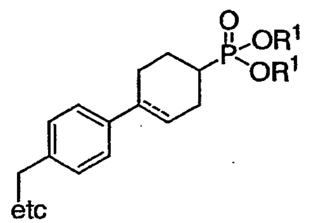


79

cycloalkyl



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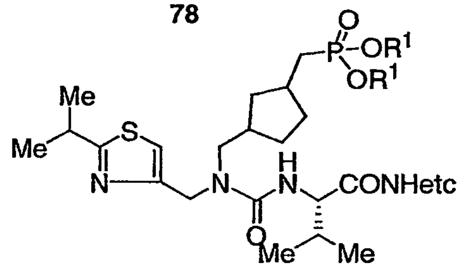
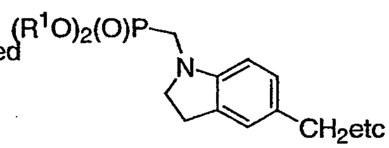


81

cyclized



82

Protection of reactive substituents.

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH].

Preparation of the phosphonate intermediates 1.

Two methods for the preparation of the phosphonate intermediate compounds **1**, in which the phosphonate moiety is attached to the isopropyl group of the carboxylic acid reactant **1.5**, are shown in Schemes **1** and **2**. The selection of the route to be employed for a given compound is made after consideration of the substituents which are present, and their stability under the reaction conditions required.

As shown in Scheme **1**, 5-amino-2-dibenzylamino-1,6-diphenyl-hexan-3-ol, **1.1**, the preparation of which is described in Org. Process Res. Dev., 1994, 3, 94, is reacted with a carboxylic acid R^2COOH **1.2**, or an activated derivative thereof, to produce the amide **1.3**.

The preparation of amides from carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274, and Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 972ff.

The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of hydroxybenztriazole, in a non-protic solvent such as, for example, pyridine, dimethylformamide or dichloromethane, to afford the amide.

Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride, anhydride, imidazolide and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane.

Preferably, the carboxylic acid **1.2** is converted into the acid chloride, and the latter compound is reacted with an equimolar amount of the amine **1.1**, in an aprotic solvent such as, for example, tetrahydrofuran, at ambient temperature. The reaction is conducted in the presence of an organic base such as triethylamine, so as to afford the amide **1.3**.

The N, N-dibenzylamino amide product **1.3** is then transformed into the free amine compound **1.4** by means of a debenzylation procedure. The deprotection of N-benzyl amines is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 365. The transformation can be effected under

reductive conditions, for example by the use of hydrogen or a hydrogen donor, in the presence of a palladium catalyst, or by treatment of the N-benzyl amine with sodium in liquid ammonia, or under oxidative conditions, for example by treatment with 3-chloroperoxybenzoic acid and ferrous chloride.

Preferably, the N, N-dibenzyl compound **1.3** is converted into the amine **1.4** by means of hydrogen transfer catalytic hydrogenolysis, for example by treatment with methanolic ammonium formate and 5% palladium on carbon catalyst, at ca. 75°C for ca. 6 hours, for example as described in U.S. Patent 5,914,332.

The thus-obtained amine **1.4** is then transformed into the amide **1.6** by reaction with the carboxylic acid **1.5**, or an activated derivative thereof, in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto. Preparations of the carboxylic acids **1.5** are described below, Schemes **13** - **15**. The amide-forming reaction is conducted under similar conditions to those described above for the preparation of the amide **1.3**.

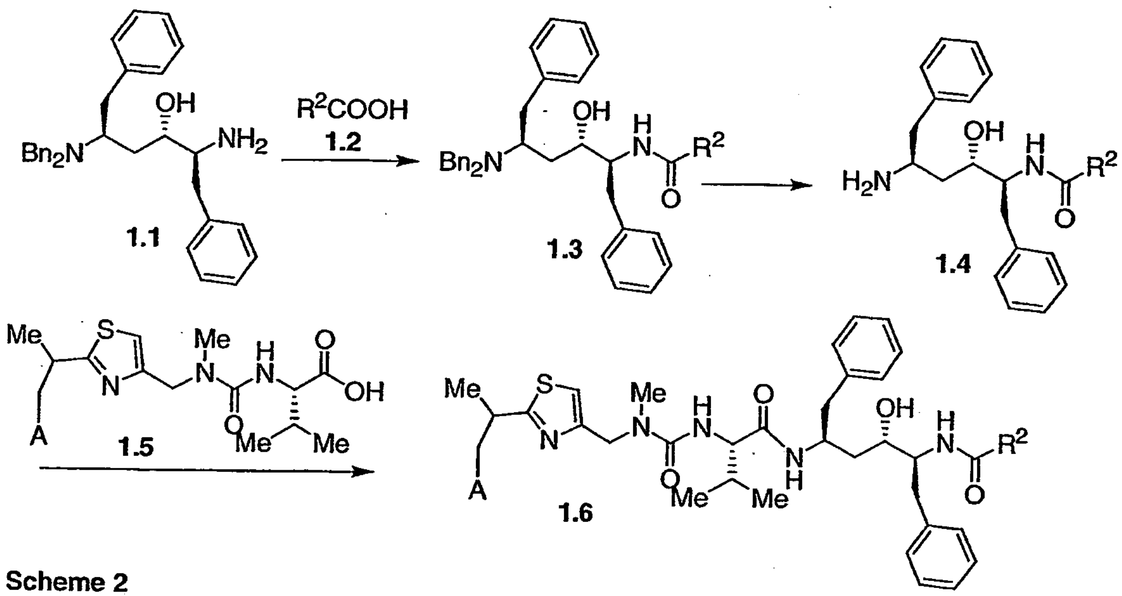
Preferably, the carboxylic acid is converted into the acid chloride, and the acid chloride is reacted with the amine **1.4** in a solvent mixture composed of an organic solvent such as ethyl acetate, and water, in the presence of a base such as sodium bicarbonate, for example as described in Org. Process Res. Dev., 2000, 4, 264, to afford the amide product **1.6**.

Scheme **2** illustrates an alternative method for the preparation of the phosphonate-containing diamides **1**. In this procedure, 2-phenyl-1-[4-phenyl-2-(1-vinyl-propenyl)-[1,3,2]oxazaborinan-6-yl]-ethylamine **2.1**, the preparation of which is described in WO 9414436, is reacted with the carboxylic acid R^2COOH **1.2**, or an activated derivative thereof, to afford the amide product **2.2**. The reaction is effected employing the same conditions as were described above for the preparation of the amide **1.3**. Preferably, equimolar amounts of the acid chloride derived from the carboxylic acid **1.2** is reacted with the amine **2.1** in a polar aprotic solvent such as tetrahydrofuran or dimethylformamide, at from ambient temperature to about -60°C, in the presence of an organic or inorganic base, to produce the amide **2.2**. The product is then reacted with the carboxylic acid **1.5**, or an activated derivative thereof, to afford the amide **1.6**. The amide-forming reaction is conducted under similar conditions to those described above for the preparation of the amide **1.3**. Preferably, the acid **1.5** and the amine **2.2** are reacted in the presence of hydroxybenztriazole, and N-ethyl-N'-dimethylaminopropyl carbodiimide, in tetrahydrofuran at ambient temperature, as described in U.S. Patent 5,484,801, to yield the amide **1.6**.

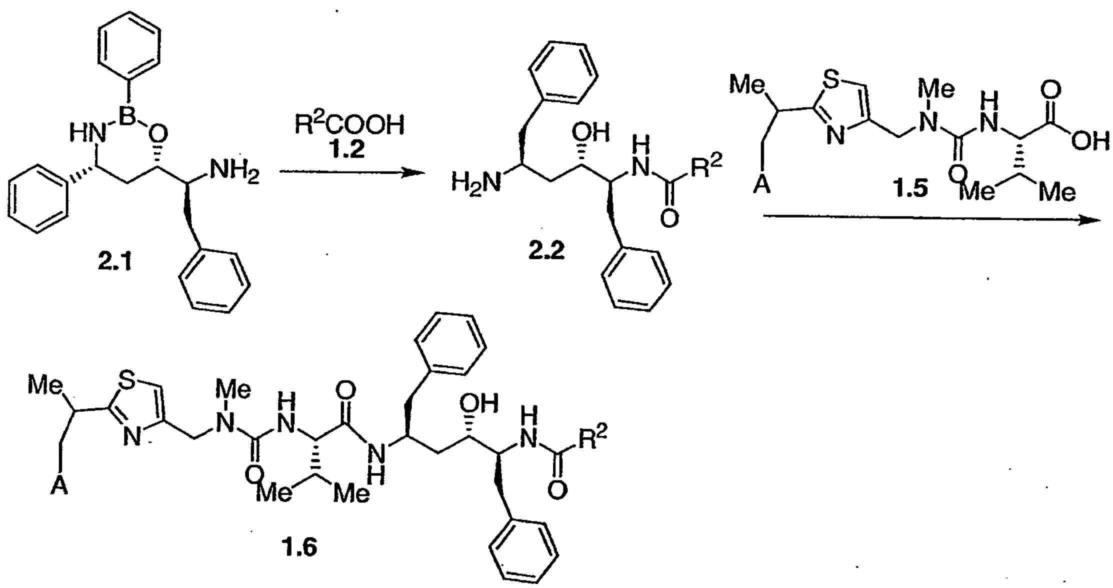
The reactions illustrated in Schemes **1** and **2** illustrate the preparation of the compounds **1.6** in which A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as, for example, optionally protected OH, SH, NH, as described below. Scheme **3** depicts the conversion of the compounds **1.6** in which A is OH, SH, NH, as described below, into the compounds **1** in which A is the group link-$P(O)(OR^1)_2$. Procedures for the conversion of the group A into the group link-P(O))$(OR^1)_2$ are described below, (Schemes **16-26**).

In this and succeeding examples, the nature of the phosphonate ester group can be varied, either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described below, (Scheme **27**)

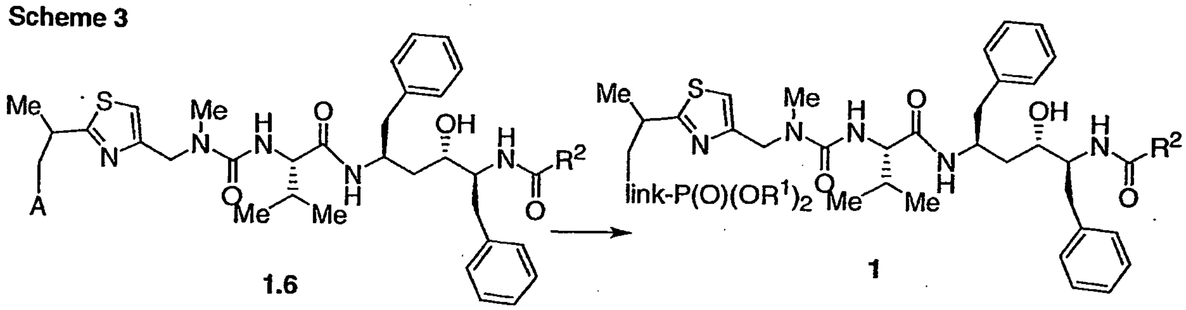
Scheme 1



Scheme 2



Scheme 3



Preparation of the phosphonate intermediates 2.

Two methods for the preparation of the phosphonate intermediate compounds **2** are shown in Schemes **4** and **5**. The selection of the route to be employed for a given compound is made after consideration of the substituents which are present, and their stability under the reaction conditions required.

As depicted in Scheme **4**, the tribenzylated phenylalanine derivative **4.1**, in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, as described below, is reacted with the anion **4.2** derived from acetonitrile, to afford the ketonitrile **4.3**. Preparations of the tribenzylated phenylalanine derivatives **4.1** are described below, Schemes **16-18**.

The anion of acetonitrile is prepared by the treatment of acetonitrile with a strong base, such as, for example, lithium hexamethyldisilylazide or sodium hydride, in an inert organic solvent such as tetrahydrofuran or dimethoxyethane, as described, for example, in U.S. Patent 5,491,253. The solution of the acetonitrile anion **4.2**, in an aprotic solvent such as tetrahydrofuran, dimethoxyethane and the like, is then added to a solution of the ester **4.1** at low temperature, to afford the coupled product **4.3**.

Preferably, a solution of ca. two molar equivalent of acetonitrile, prepared by the addition of ca. two molar equivalent of sodium amide to a solution of acetonitrile in tetrahydrofuran at -40°C, is added to a solution of one molar equivalent of the ester **4.1** in tetrahydrofuran at -40°C, as described in J. Org. Chem., 1994, 59, 4040, to produce the ketonitrile **4.3**.

The above-described ketonitrile compound **4.3** is then reacted with an organometallic benzyl reagent **4.4**, such as a benzyl Grignard reagent or benzyllithium, to afford the ketoenamine **4.5**. The reaction is conducted in an inert aprotic organic solvent such as diethyl ether, tetrahydrofuran or the like, at from -80°C to ambient temperature.

Preferably, the ketonitrile **4.3** is reacted with three molar equivalents of benzylmagnesium chloride in tetrahydrofuran at ambient temperature, to produce, after quenching by treatment with an organic carboxylic acid such as citric acid, as described in J. Org. Chem., 1994, 59, 4040, the ketoenamine **4.5**.

The ketoenamine **4.5** is then reduced, in two stages, via the ketoamine **4.6**, to produce the amino alcohol **4.7**. The transformation of the ketoenamine **4.5** to the aminoalcohol **4.7** can be

effected in one step, or in two steps, with or without isolation of the intermediate ketoamine **4.6**, as described in U.S. Patent 5,491,253.

For example, the ketoenamine **4.5** is reduced with a boron-containing reducing agent such as sodium borohydride, sodium cyanoborohydride and the like, in the presence of an acid such as methanesulfonic acid, as described in J. Org. Chem., 1994, 59, 4040, to afford the ketoamine **4.6**. The reaction is performed in an ethereal solvent such as, for example, tetrahydrofuran or methyl tert-butyl ether. The latter compound is then reduced with sodium borohydride-trifluoroacetic acid, as described in U.S. Patent 5,491,253, to afford the aminoalcohol **4.7**.

Alternatively, the ketoenamine **4.5** can be reduced to the aminoalcohol **4.7** without isolation of the intermediate ketoamine **4.6**. In this procedure, described in U.S. Patent 5,491,253, the ketoenamine **4.5** is reacted with sodium borohydride-methanesulfonic acid, in an ethereal solvent such as dimethoxyethane and the like. The reaction mixture is then treated with a quenching agent such as triethanolamine, and the procedure is continued by the addition of sodium borohydride and a solvent such as dimethyl formamide or dimethylacetamide or the like, to afford the aminoalcohol **4.7**.

The aminoalcohol **4.7** is converted into the amide **4.9** by reaction with the acid R^3COOH **4.8**, or an activated derivative thereof, to produce the amide **4.9**. This reaction is conducted under similar conditions to those described above for the preparation of the amides **1.3** and **1.6**.

The dibenzylated amide product **4.9** is deprotected to afford the free amine **4.10**. The conditions for the debenzylation reaction are the same as those described above for the deprotection of the dibenzyl amine **1.3** to yield the amine **1.4**, (Scheme **1**).

The amine **4.10** is then reacted with the carboxylic acid R^2COOH **1.2**, or an activated derivative thereof, to produce the amide **4.11**. This reaction is conducted under similar conditions to those described above for the preparation of the amides **1.3** and **1.6**.

Alternatively, the amide **4.11** can be prepared by means of the sequence of reactions illustrated in Scheme **5**.

In this sequence, the tribenzylated amino acid derivative **4.1** is converted, by means of the reaction sequence shown in Scheme **4** into the dibenzylated amine **4.7**. This compound is then converted into a protected derivative, for example the tert-butoxycarbonyl (BOC) derivative **5.1**. Methods for the conversion of amines into the BOC derivative are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990,

p. 327. For example, the amine can be reacted with di-tert-butoxycarbonylanhydride (BOC anhydride) and a base, or with 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON), and the like.

Preferably, the amine is reacted with ca. 1.5 molar equivalents of BOC anhydride and excess potassium carbonate, in methyl tert-butyl ether, at ambient temperature, for example as described in U.S. Patent 5,914,3332, to yield the BOC-protected product **5.1**.

The N-benzyl protecting groups are then removed from the amide product **5.1** to afford the free amine **5.2**. The conditions for this transformation are similar to those described above for the preparation of the amine **1.4**, (Scheme **1**).

Preferably, the N, N-dibenzyl compound **5.1** is converted into the amine **5.2** by means of hydrogen transfer catalytic hydrogenolysis, for example by treatment with methanolic ammonium formate and 5% palladium on carbon catalyst, at ca. 75°C for ca. 6 hours, for example as described in U.S. Patent 5,914,332.

The amine compound **5.2** is then reacted with the carboxylic acid R^2COOH **1.2**, or an activated derivative thereof, to produce the amide **5.3**. This reaction is conducted under similar conditions to those described above for the preparation of the amides **1.3** and **1.6**, to afford the amide product **5.3**.

The latter compound is then converted into the amine **5.4** by removal of the BOC protecting group. The removal of BOC protecting groups is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 328. The deprotection can be effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride or trifluoroacetic acid, or by reaction with trimethylsilyl iodide or aluminum chloride.

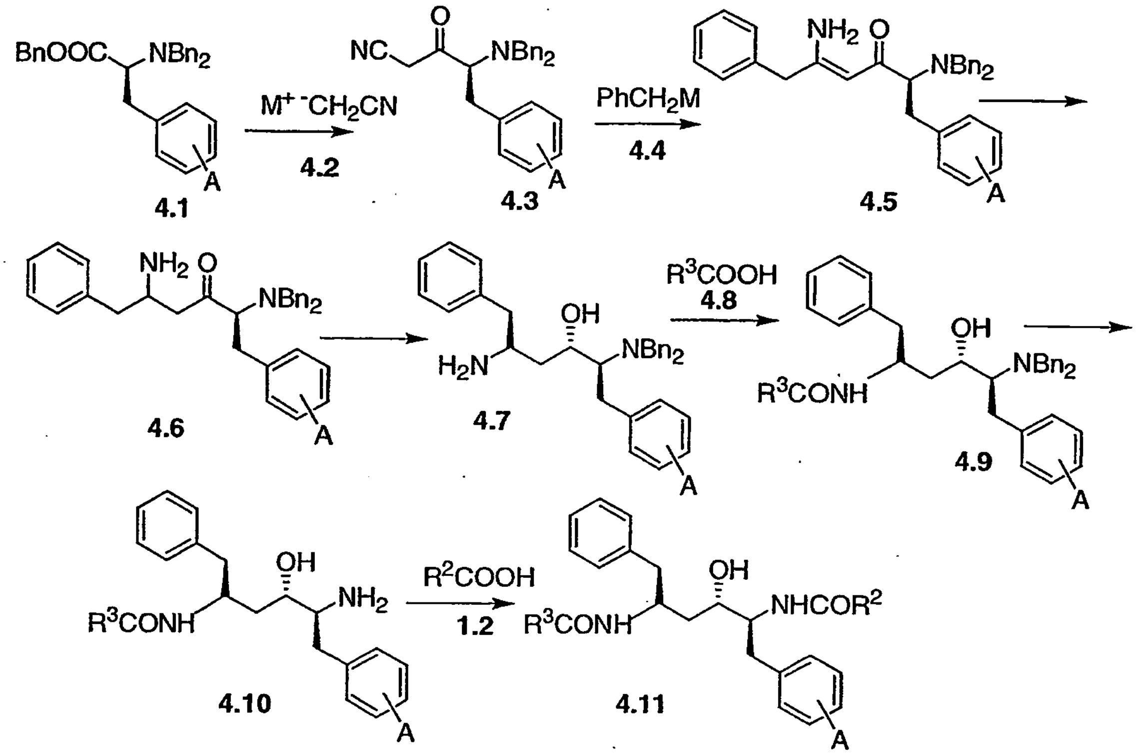
Preferably, the BOC group is removed by treatment of the substrate **5.3** with trifluoroacetic acid in dichloromethane at ambient temperature, for example as described in U.S. Patent 5,914,232, to afford the free amine product **5.4**.

The free amine thus obtained is then reacted with the carboxylic acid R^3COOH **4.8**, or an activated derivative thereof, to produce the amide **4.11**. This reaction is conducted under similar conditions to those described above for the preparation of the amides **1.3** and **1.6**.

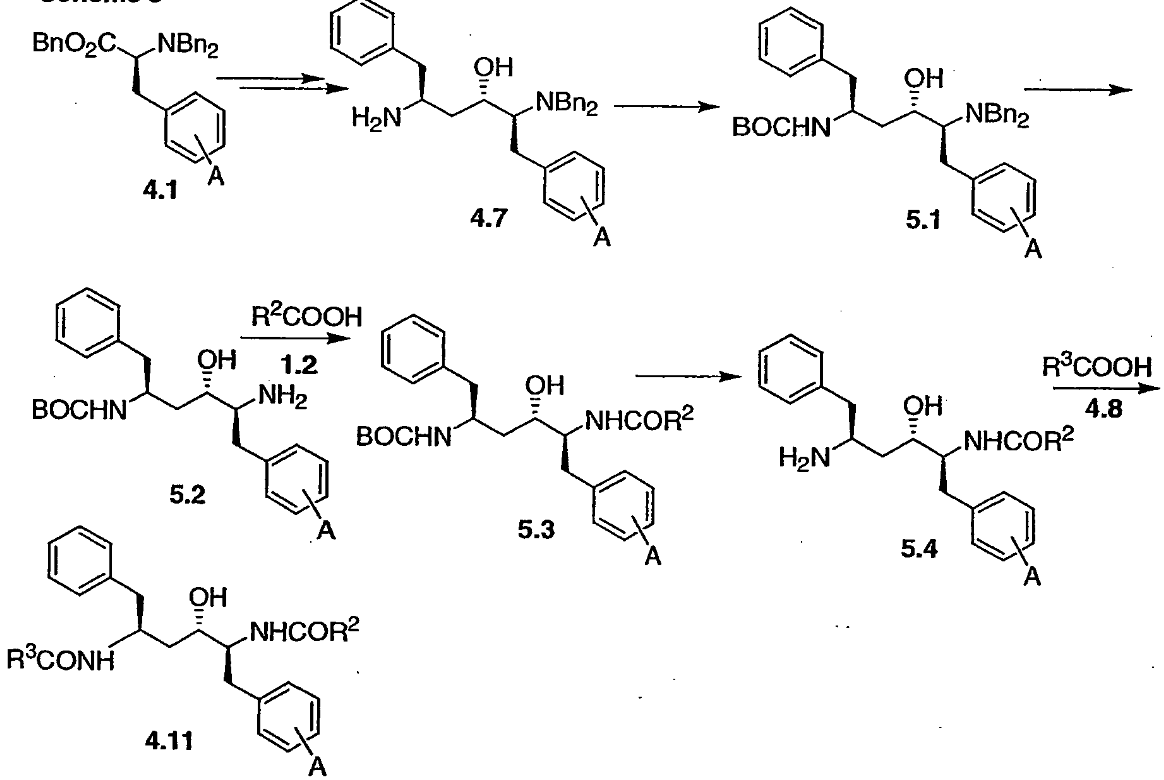
The reactions shown in Schemes **4** and **5** illustrate the preparation of the compounds **4.11** in which A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as, for example,

optionally protected OH, SH, NH, as described below. Scheme **6** depicts the conversion of the compounds **4.11** in which A is OH, SH, NH, as described below, into the compounds **2**. Procedures for the conversion of the group A into the group link-P(O))(OR^1)$_2$ are described below, (Schemes **16-26**).

Scheme 4



Scheme 5



Preparation of the phosphonate intermediates 3.

The phosphonate ester intermediate compounds **3** can be prepared by two alternative methods, illustrated in Schemes **7** and **8**. The selection of the route to be employed for a given compound is made after consideration of the substituents which are present, and their stability under the reaction conditions required.

As shown in Scheme **7**, 4-dibenzylamino-3-oxo-5-phenyl-pentanenitrile **7.1**, the preparation of which is described in J. Org. Chem., 1994, 59, 4040, is reacted with a substituted benzylmagnesium halide reagent **7.2**, in which the group B is a substituent, protected if appropriate, which can be converted, during or after the sequence of reactions shown in Scheme **7**, into the moiety link-$P(O)(OR^1)_2$. Examples of the substituent B are Br, [OH], [SH], [NH_2] and the like; procedures for the transformation of these groups into the phosphonate moiety are shown below in Schemes **16-26**. The conditions for the reaction between the benzylmagnesium halide and the ketonitrile are similar to those described above for the preparation of the ketoenamine **4.5** (Scheme **4**).

Preferably, the ketonitrile **7.1** is reacted with three molar equivalents of the substituted benzylmagnesium chloride **7.2** in tetrahydrofuran at ambient temperature, to produce, after quenching by treatment with an organic carboxylic acid such as citric acid, as described in J. Org. Chem., 1994, 59, 4040, the ketoenamine **7.3**.

The thus-obtained ketoenamine **7.3** is then transformed, via the intermediate compounds **7.4**, **7.5**, **7.6**, and **7.7** into the diacylated carbinol **7.8**. The conditions for each step in the conversion of the ketoenamine **7.3** to the diacylated carbinol **7.8** are the same as those described above (Scheme **4**) for the transformation of the ketoenamine **4.5** into the diacylated carbinol **4.11**.

The diacylated carbinol **7.8** is then converted into the phosphonate ester **3**, using procedures illustrated below in Schemes **16-26**.

Alternatively, the phosphonate esters **3** can be obtained by means of the reactions illustrated in Scheme **8**. In this procedure, the amine **7.5**, the preparation of which is described above, (Scheme 7) is converted into the BOC derivative **8.1**. The conditions for the introduction of

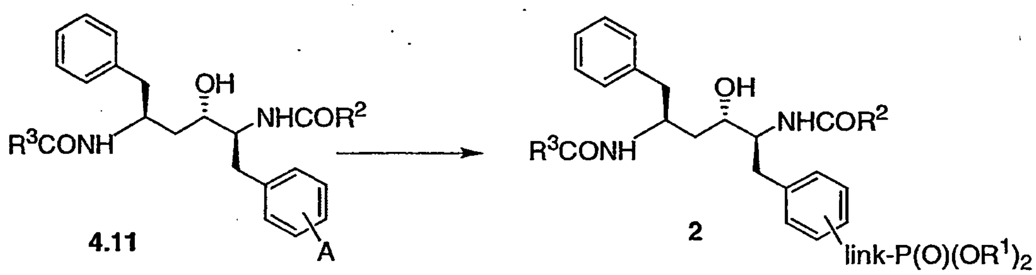
the BOC group are similar to those described above for the protection of the amine **5.1**, (Scheme **5**).

Preferably, the amine is reacted with ca. 1.5 molar equivalents of BOC anhydride and excess potassium carbonate, in methyl tert-butyl ether, at ambient temperature, for example as described in U.S. Patent 5,914,332, to yield the BOC-protected product **8.1**.

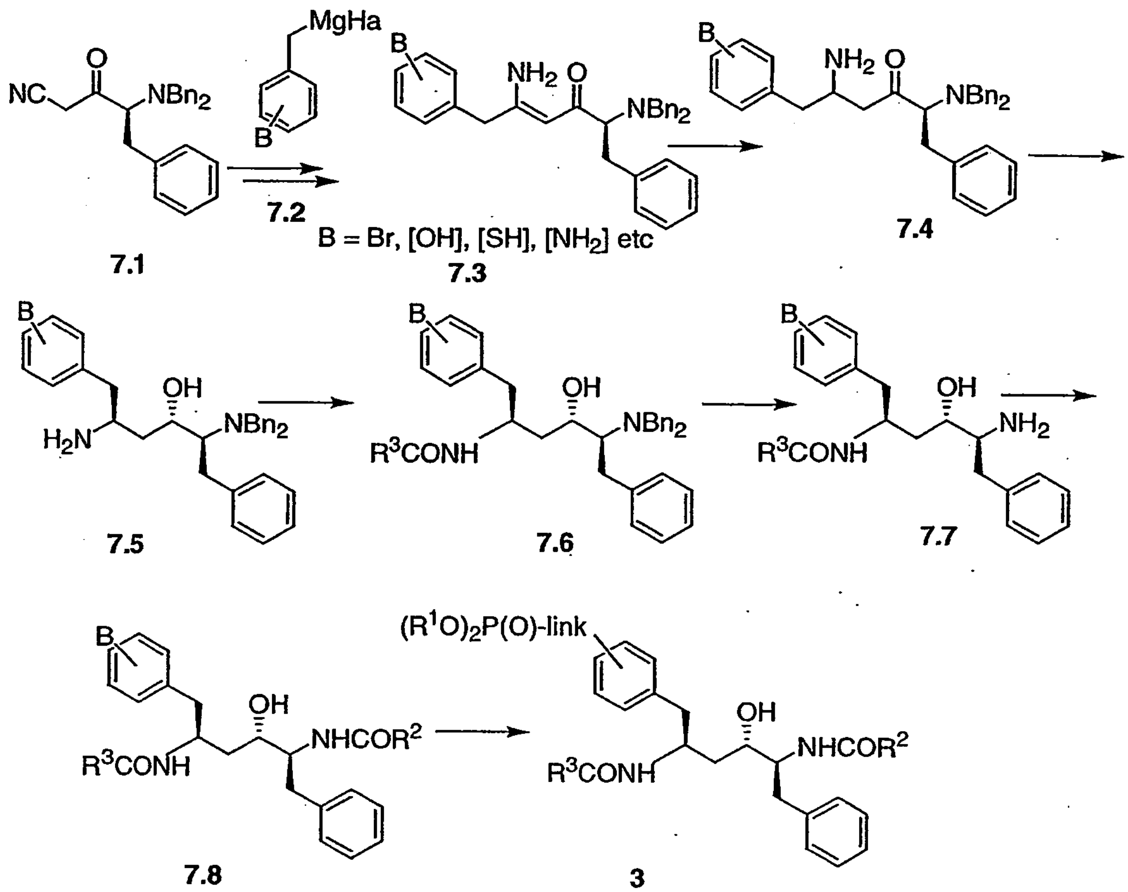
The BOC-protected amine **8.1** is then converted, via the intermediates **8.2**, **8.3** and **8.4** into the diacylated carbinol **8.5**. The reaction conditions for this sequence of reactions are similar to those described above for the transformation of the BOC-protected amine **5.1** into the diacylated carbinol **5.4** (Scheme **5**).

The diacylated carbinol **8.5** is then converted into the phosphonate ester **3**, using procedures illustrated below in Schemes **16-26**.

Scheme 6

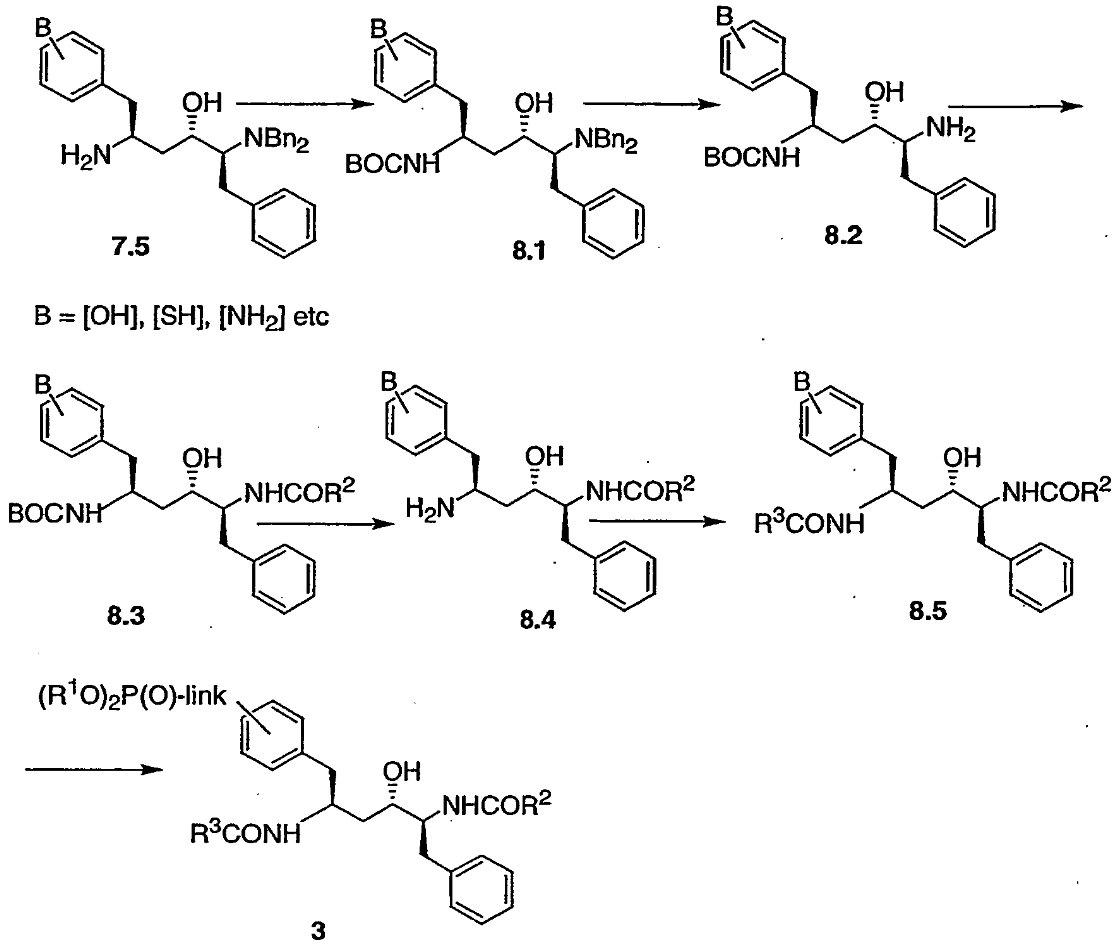


Scheme 7



NC
O
NBn2
MgHa
B
7.1
7.2
B = Br, [OH], [SH], [NH2] etc
7.3
NH2
7.4
7.5
7.6
7.7
7.8
3
OH
H2N
R3CONH
NH2
NHCOR2
(R1O)2P(O)-link

Scheme 8



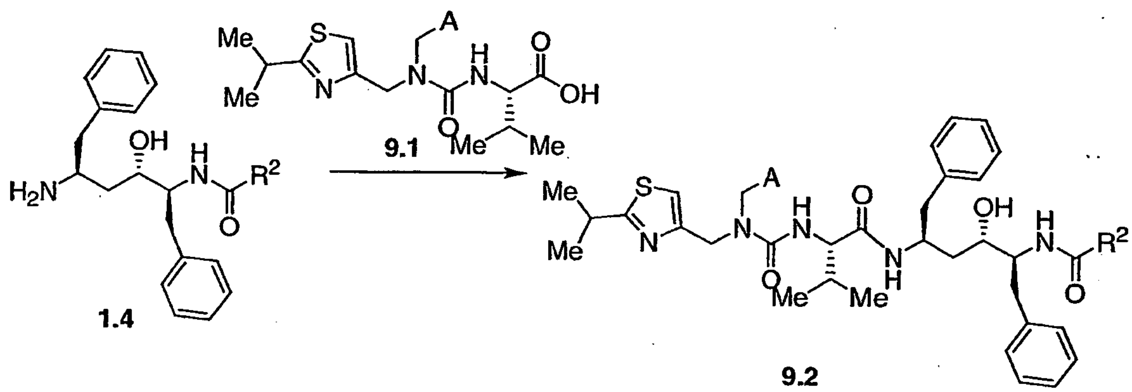
Preparation of the phosphonate intermediates 4.

Scheme **9** illustrates the preparation of the intermediate phosphonate esters **9.2** in which the substituent A, which is the phosphonate ester moiety or a precursor group thereto, is attached to one of the urea nitrogen atoms in the carboxylic acid reactant **9.1**. The preparation of the carboxylic acid reactant **9.1** is described below, Schemes **24-25**. In this procedure, the amine **1.4**, prepared as described in Scheme **1**, is reacted with the carboxylic acid **9.1**, to afford the amide **9.2**. The reaction between the amine **1.4** and the carboxylic acid **9.1**, or an activated derivative thereof, is conducted under the same general conditions as those described above for the preparation of the amide **1.6** (Scheme **1**). Preferably, the reactants are combined in the

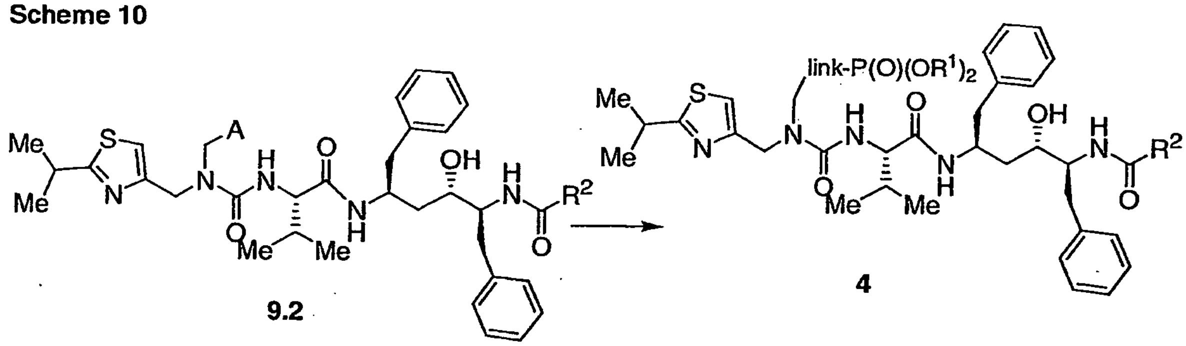
presence of hydroxybenztriazole and a carbodiimide, as described in U.S. Patent 5,484,801, to yield the amide product **9.2**.

The procedure shown in Scheme **9** describes the preparation of the compounds **9.2** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor group thereto, such as [OH], [SH, [NH], as described below. Scheme **10** depicts the conversion of compounds **9.2** in which A is [OH], [SH, [NH], into the compounds **4**, in which the group A has been transformed into the group link-P(O)(OR^1)$_2$. The methods for accomplishing this transformation are described below, Schemes **16-26**.

Scheme 9



Scheme 10



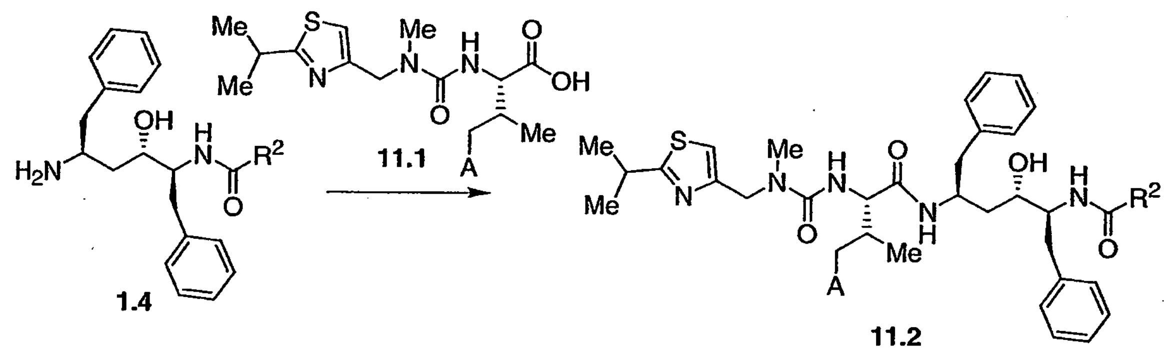
Preparation of the phosphonate intermediates 5.

Scheme **11** illustrates the preparation of the intermediate phosphonate esters **11.2** in which the substituent A, which is the phosphonate ester moiety or a precursor group thereto, is attached to the valine moiety in the carboxylic acid reactant **11.1**. The preparation of the carboxylic acid reactant **11.1** is described below, Scheme **26**. The reaction between the amine **1.4** and the

carboxylic acid **11.1**, or an activated derivative thereof, is conducted under the same general conditions as those described above for the preparation of the amide **1.3** (Scheme **1**). Preferably, the reactants are combined in the presence of hydroxybenztriazole and a carbodiimide, as described in U.S. Patent 5,484,801, to yield the amide product **11.2**.

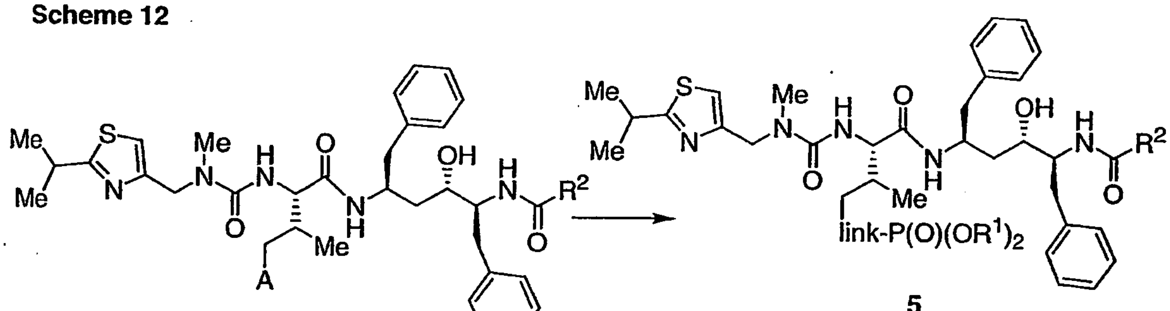
The procedure shown in Scheme **11** describes the preparation of the compounds **11.2** in which the substituent A is either the group link-P(O)(OR[1])$_2$ or a precursor group thereto, such as [OH], [SH, [NH] Ha, as described below,. Scheme **12** depicts the conversion of compounds **11.2** in which A is [OH], [SH, [NH] Br, into the compounds **5**, in which the group A has been transformed into the group link-P(O)(OR[1])$_2$. The methods for accomplishing this transformation are described below, Schemes **16-26**.

Scheme 11



1.4 11.1 11.2

Scheme 12



11.2 5

Preparation of carboxylic acids 1.5, with a phosphonate moiety attached to the isopropyl group.

Scheme **13** illustrates the preparation of carboxylic acid reactants **1.5**, in which a substituent A, attached to the isopropyl group, is either the group link-$P(O)(OR^1)_2$ or a precursor group thereto, such as [OH], [SH, [NH] Br. During the series of reaction shown in Scheme **13**, the group A may, at an appropriate stage, be converted into the group link-$P(O)(OR^1)_2$, according to the knowledge of one skilled in the art. Alternatively, the carboxylic acid **1.5**, in which A is link-$P(O)(OR^1)_2$, may be incorporated into the diamide compounds **1.6**, as described above, (Schemes **1** and **2**) before effecting the transformation of the group A into the group link-$P(O)(OR^1)_2$.

As shown in Scheme **13**, a substituted derivative of isobutyramide **13.1** is converted into the corresponding thioamide **13.2**. The conversion of amides into thioamides is described in Synthetic Organic Chemistry, by R. B. Wagner and H. D. Zook, Wiley, 1953, p. 827. The amide is reacted with a sulfur-containing reagent such as phosphorus pentasulfide or Lawessson's reagent, as described in Reagents for Organic Synthesis, by L. F. Fieser and M. Fieser, Wiley, Vol. 13, p. 38, to yield the thioamide **13.2**. Preferably, the amide **13.1** is reacted with phosphorus pentasulfide in ether solution, at ambient temperature, as described in U.S. Patent 5,484,801, to afford the amide **13.2**. The latter compound is then reacted with 1,3-dichloroacetone **13.3** to produce the substituted thiazole **13.4**. The preparation of thiazoles by the reaction between a thioamide and a chloroketone is described, for example, in Heterocyclic Chemistry, by T. A. Gilchrist, Longman, 1997, p. 321. Preferably, equimolar amounts of the reactants are combined in acetone solution at reflux temperature, in the presence of magnesium sulfate, as described in U.S. Patent 5,484,801, to produce the thiazole product **13.4**. The chloromethyl thiazole **13.4** is then reacted with methylamine to afford the substituted methylamine **13.6**. The preparation of amines by the reaction of amines with alkyl halides is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 397. Typically, the components are reacted together in a polar solvent such as an alkanol or dimethylformamide and the like. Preferably, the chloro compound **13.4** is reacted with excess aqueous methylamine at ambient temperature, as described in U.S. Patent 5,484,801, to afford the amine product **13.6**. The amine is then converted into the urea

derivative **13.8** by reaction with an activated derivative of the valine carbamic acid **13.7**, in which X is a leaving group such as alkanoyloxy or 4-nitrophenoxy. The preparation of ureas by the reaction between carbamic acid derivatives and amines is described in Chem. Rev., 57, 47, 1957. Suitable carbamic acid derivatives are prepared by the reaction between an amine and an alkyl or aryl chloroformate, for example as described in WO 9312326. Preferably, the reaction is performed using carbamic acid derivative **13.7**, in which X is 4-nitrophenoxy, and the amine **13.8**; the reaction is conducted at about 0°C in an inert solvent such as dichloromethane, in the presence of an organic base such as dimethylaminopyridine or N-methylmorpholine, as described in U.S. Patent 5,484,801, to yield the urea product **13.8**. The ester group present in the urea product **13.8** is then hydrolyzed to afford the corresponding carboxylic acid **1.5**. Hydrolysis methods for converting esters into carboxylic acids are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 981. The methods include the use of enzymes such as pig liver esterase, and chemical methods such as the use of alkali metal hydroxides in aqueous organic solvent mixtures. Preferably, the methyl ester is hydrolyzed by treatment with lithium hydroxide in aqueous dioxan, as described in U.S. Patent 5,848,801, to yield the carboxylic acid **1.5**.

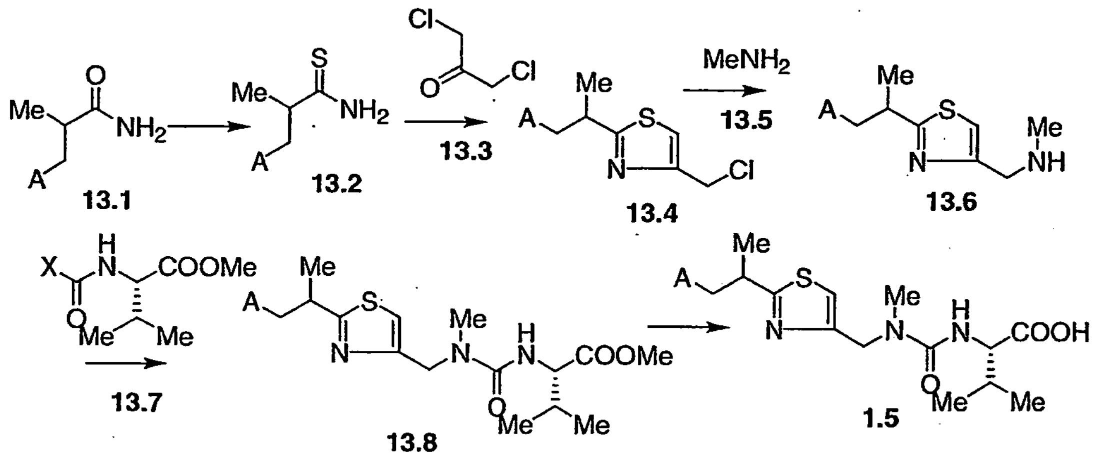
Scheme **14** illustrates the preparation of the carboxylic acids **9.1** in which the group A, attached to the amine moiety, is either the group link-$P(O)(OR^1)_2$ or a precursor group thereto, such as [OH], [SH, [NH] Br. During the series of reaction shown in Scheme **14**, the group A may, at an appropriate stage, be converted into the group link-$P(O)(OR^1)_2$, according to the knowledge of one skilled in the art. Alternatively, the carboxylic acid **9.1**, in which A is link-$P(O)(OR^1)_2$, may be incorporated into the diamide compounds **9.2**, as described above, (Scheme **9**) before effecting the transformation of the group A into the group link-$P(O)(OR^1)_2$.

As shown in Scheme **14**, 4-chloromethyl-2-isopropyl-thiazole **14.1**, prepared as described in WO 9414436, is reacted with an amine **14.2**, in which A is as described above, to afford the amine **13.6**. The conditions for the alkylation reaction are the same as those described above for the preparation of the amine **13.6**. The product is then transformed, via the intermediate ester **14.4**, into the carboxylic acid **9.1**. The conditions for the reactions required to transform the amine **14.3** into the carboxylic acid **9.1** are the same as those described above (Scheme **13**) for the analogous chemical steps.

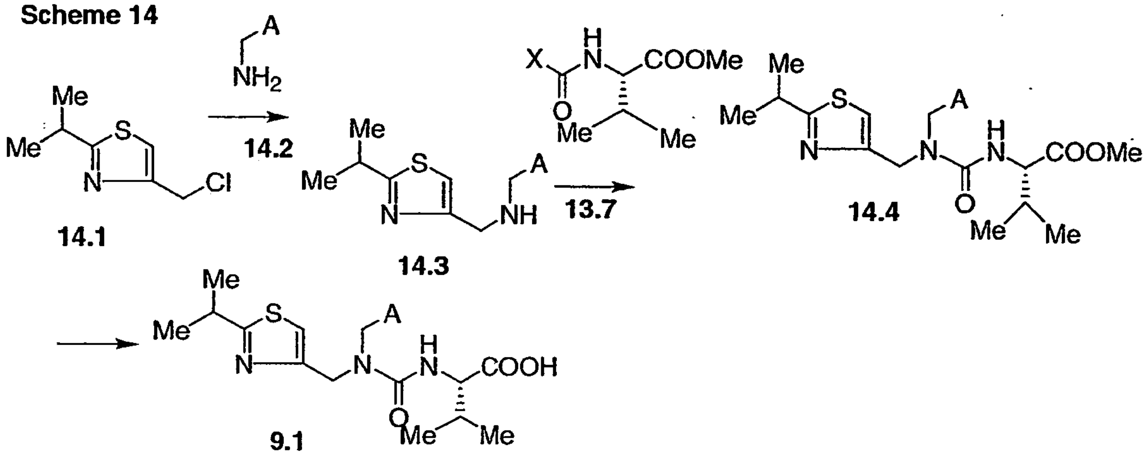
Scheme **15** illustrates the preparation of the carboxylic acids **11.1** in which the group A, attached to the valine moiety, is either the group link-P(O)(OR^1)$_2$ or a precursor group thereto, such as [OH], [SH, [NH] Br. During the series of reaction shown in Scheme **15**, the group A may, at an appropriate stage, be converted into the group link-P(O)(OR^1)$_2$, according to the knowledge of one skilled in the art. Alternatively, the carboxylic acid **11.1**, in which A is link-P(O)(OR^1)$_2$ may be incorporated into the diamide compounds **11.2**, as described above, (Scheme **11**) before effecting the transformation of the group A into the group link-P(O)(OR^1)$_2$.

As shown in Scheme **15**, (2-isopropyl-thiazol-4-ylmethyl)-methyl-amine, **15.1**, prepared as described in WO 9414436, is reacted with a substituted valine derivative **15.2**, in which the group A is as defined above. Methods for the preparation of the valine derivatives **15.2** are described below, Scheme **26**. The resultant ester **15.3** is then hydrolyzed, as described above, to afford the carboxylic acid **11.1**

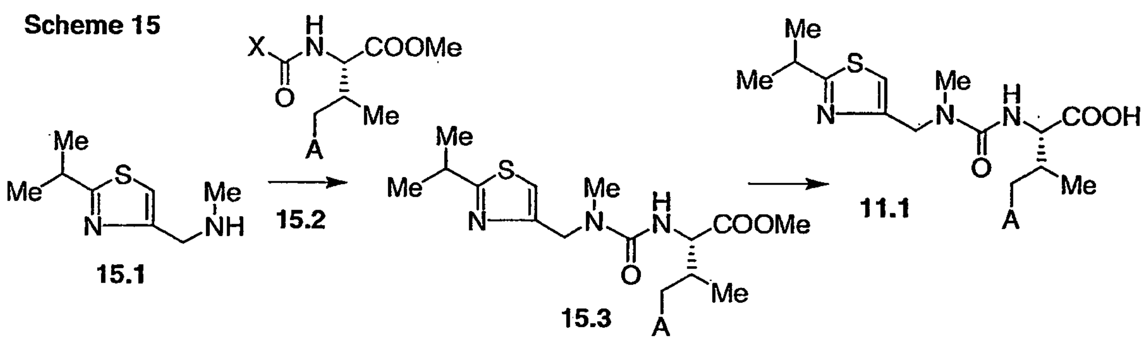
Scheme 13



Scheme 14



Scheme 15



Preparation of phenylalanine derivatives 4.1 incorporating phosphonate moieties.

Scheme **16** illustrates the preparation of phenylalanine derivatives incorporating phosphonate moieties attached to the phenyl ring by means of a heteroatom and an alkylene chain. The compounds are obtained by means of alkylation or condensation reactions of hydroxy or mercapto-substituted phenylalanine derivatives **16.1**.

In this procedure, a hydroxy or mercapto-substituted phenylalanine is converted into the benzyl ester **16.2**. The conversion of carboxylic acids into esters is described for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 966. The conversion can be effected by means of an acid-catalyzed reaction between the carboxylic acid and benzyl alcohol, or by means of a base-catalyzed reaction between the carboxylic acid and a benzyl halide, for example benzyl chloride. The hydroxyl or mercapto substituent present in the benzyl ester **16.2** is then protected. Protection methods for phenols and thiols are described respectively, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p 277. For example, suitable protecting groups for phenols and thiophenols include tert-butyldimethylsilyl or tert-butyldiphenylsilyl. Thiophenols may also be protected as S-adamantyl groups, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 289. The protected hydroxy- or mercapto ester **16.3** is then reacted with a benzyl or substituted benzyl halide and a base, for example as described in U.S. Patent 5,491,253, to afford the N, N-dibenzyl product **16.4**. For example, the amine **16.3** is reacted at ca. 90°C with two molar equivalents of benzyl chloride in aqueous ethanol containing potassium carbonate, to afford the tribenzylated product **16.4**, as described in U.S. Patent 5,491,253. The protecting group present on the O or S substituent is then removed. Removal of O or S protecting groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 277. For example, silyl protecting groups are removed by treatment with tetrabutylammonium fluoride and the like, in a solvent such as tetrahydrofuran at ambient temperature, as described in J. Am. Chem. Soc., 94, 6190, 1972. S-Adamantyl groups can be removed by treatment with mercuric trifluoroacetate in acetic acid, as described in Chem. Pharm. Bull., 26, 1576, 1978.

The resultant phenol or thiophenol **16.5** is then reacted under various conditions to provide protected phenylalanine derivatives **16.9**, **16.10** or **16.11**, incorporating phosphonate moieties attached by means of a heteroatom and an alkylene chain.

In this step, the phenol or thiophenol **16.5** is reacted with a dialkyl bromoalkyl phosphonate **16.6** to afford the product **16.9**. The alkylation reaction between **16.5** and **16.6** is effected in the presence of an organic or inorganic base, such as, for example, diazabicyclononene, cesium carbonate or potassium carbonate, The reaction is performed at from ambient temperature to ca. 80°C, in a polar organic solvent such as dimethylformamide or acetonitrile, to afford the ether or thioether product **16.9**.

For example, as illustrated in Scheme **16**, Example 1, a hydroxy-substituted phenylalanine derivative such as tyrosine, **16.12** is converted, as described above, into the benzyl ester **16.13**. The latter compound is then reacted with one molar equivalent of chloro tert-butyldimethylsilane, in the presence of a base such as imidazole, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford the silyl ether **16.14**. This compound is then converted, as described above, into the tribenzylated derivative **16.15**. The silyl protecting group is removed by treatment of **16.15** with a tetrahydrofuran solution of tetrabutyl ammonium fluoride at ambient temperature, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford the phenol **16.16**. The latter compound is then reacted in dimethylformamide at ca. 60°C, with one molar equivalent of a dialkyl 3-bromopropyl phosphonate **16.17** (Aldrich), in the presence of cesium carbonate, to afford the alkylated product **16.18**.

Using the above procedures, but employing, in place of the hydroxy-substituted phenylalanine derivative **16.12**, different hydroxy or thio-substituted phenylalanine derivatives **16.1**, and/or different bromoalkyl phosphonates **16.6**, the corresponding ether or thioether products **16.9** are obtained.

Alternatively, the hydroxy or mercapto-substituted tribenzylated phenylalanine derivative **16.5** is reacted with a dialkyl hydroxymethyl phosphonate **16.7** under the conditions of the Mitsonobu reaction, to afford the ether or thioether compounds **16.10**. The preparation of aromatic ethers by means of the Mitsonobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4. The phenol or thiophenol and the alcohol component are reacted together in an

aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products **16.10**. For example, as shown in Scheme **16**, Example 2, 3-mercaptophenylalanine **16.19**, prepared as described in WO 0036136, is converted, as described above, into the benzyl ester **16.20**. The resultant ester is then reacted in tetrahydrofuran solution with one molar equivalent of 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in Bull. Chem. Soc. Jpn., 37, 433, 1974, to afford the 4-methoxybenzyl thioether **16.21**. This compound is then converted, as described above for the preparation of the compound **16.4**, into the tribenzyl derivative **16.22**. The 4-methoxybenzyl group is then removed by the reaction of the thioether **16.22** with mercuric trifluoroacetate and anisole in trifluoroacetic acid, as described in J.Org. Chem., 52, 4420, 1987, to afford the thiol **16.23**. The latter compound is reacted, under the conditions of the Mitsonobu reaction, with diethyl hydroxymethyl phosphonate **16.7**, diethylazodicarboxylate and triphenylphosphine, for example as described in Synthesis, 4, 327, 1998, to yield the thioether product **16.24**.

Using the above procedures, but employing, in place of the mercapto-substituted phenylalanine derivative **16.19**, different hydroxy or mercapto-substituted phenylalanines **16.1**, and/or different dialkylhydroxymethyl phosphonates **16.7**, the corresponding products **16.10** are obtained.

Alternatively, the hydroxy or mercapto-substituted tribenzylated phenylalanine derivative **16.5** is reacted with an activated derivative of a dialkyl hydroxymethylphosphonate **16.8** in which Lv is a leaving group. The components are reacted together in a polar aprotic solvent such as, for example, dimethylformamide or dioxan, in the presence of an organic or inorganic base such as triethylamine or cesium carbonate, to afford the ether or thioether products **16.11**. For example, as illustrated in Scheme **16**, Example 3, 3-hydroxyphenylalanine **16.25** (Fluka) is converted, using the procedures described above, into the tribenzylated compound **16.26**. The latter compound is reacted, in dimethylformamide at ca. 50°C, in the presence of potassium carbonate, with diethyl trifluoromethanesulfonyloxymethylphosphonate **16.27**, prepared as described in Tet. Lett., 1986, 27, 1477, to afford the ether product **16.28**.

Using the above procedures, but employing, in place of the hydroxy-substituted phenylalanine derivative **16.25**, different hydroxy or mercapto-substituted phenylalanines **16.1**, and/or different dialkyl trifluoromethanesulfonyloxymethylphosphonates **16.8**, the corresponding products **16.11** are obtained.

Scheme **17** illustrates the preparation of phenylalanine derivatives incorporating phosphonate moieties attached to the phenyl ring by means of an alkylene chain incorporating a nitrogen atom. The compounds are obtained by means of a reductive alkylation reaction between a formyl-substituted tribenzylated phenylalanine derivative **17.3** and a dialkyl aminoalkylphosphonate **17.4**.

In this procedure, a hydroxymethyl-substituted phenylalanine **17.1** is converted into the tribenzylated derivative **17.2** by reaction with three equivalents of a benzyl halide, for example, benzyl chloride, in the presence of an organic or inorganic base such as diazabicyclononene or potassium carbonate. The reaction is conducted in a polar solvent optionally in the additional presence of water. For example, the aminoacid **17.1** is reacted with three equivalents of benzyl chloride in aqueous ethanol containing potassium carbonate, as described in U.S. Patent 5,491,253, to afford the product **17.2**. The latter compound is then oxidized to afford the corresponding aldehyde **17.3**. The conversion of alcohols to aldehydes is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 604ff. Typically, the alcohol is reacted with an oxidizing agent such as pyridinium chlorochromate, silver carbonate, or dimethyl sulfoxide/acetic anhydride, to afford the aldehyde product **17.3**. For example, the carbinol **17.2** is reacted with phosgene, dimethyl sulfoxide and triethylamine, as described in J. Org. Chem., 43, 2480, 1978, to yield the aldehyde **17.3**. This compound is reacted with a dialkyl aminoalkylphosphonate **17.4** in the presence of a suitable reducing agent to afford the amine product **17.5**. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in J. Org. Chem., 55, 2552, 1990.

For example, 3-(hydroxymethyl)-phenylalanine **17.6**, prepared as described in Acta Chem. Scand. Ser. B, 1977, B31, 109, is converted, as described above, into the formylated derivative **17.7**. This compound is then reacted with a dialkyl aminoethylphosphonate **17.8**,

prepared as described in J. Org. Chem., 200, 65, 676, in the presence of sodium cyanoborohydride, to produce the alkylated product **17.9**.

Using the above procedures, but employing, in place of 3-(hydroxymethyl)-phenylalanine **17.6**, different hydroxymethyl phenylalanines **17.1**, and/or different aminoalkyl phosphonates **17.4**, the corresponding products **17.5** are obtained.

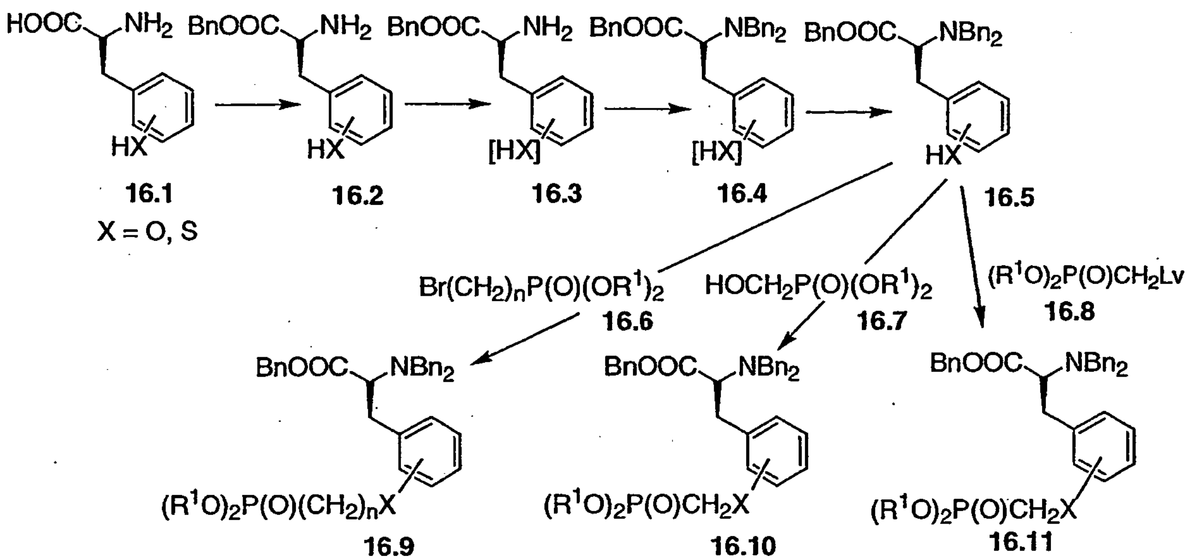
Scheme **18** depicts the preparation of phenylalanine derivatives in which a phosphonate moiety is attached directly to the phenyl ring. In this procedure, a bromo-substituted phenylalanine **18.1** is converted, as described above, (Scheme **17**) into the tribenzylated derivative **18.2**. The product is then coupled, in the presence of a palladium(0) catalyst, with a dialkyl phosphite **18.3** to produce the phosphonate ester **18.4**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992.

For example, 3-bromophenylalanine **18.5**, prepared as described in Pept. Res., 1990, 3, 176, is converted, as described above, (Scheme **17**) into the tribenzylated compound **18.6**. This compound is then reacted, in toluene solution at reflux, with diethyl phosphite **18.7**, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to afford the phosphonate product **18.8**.

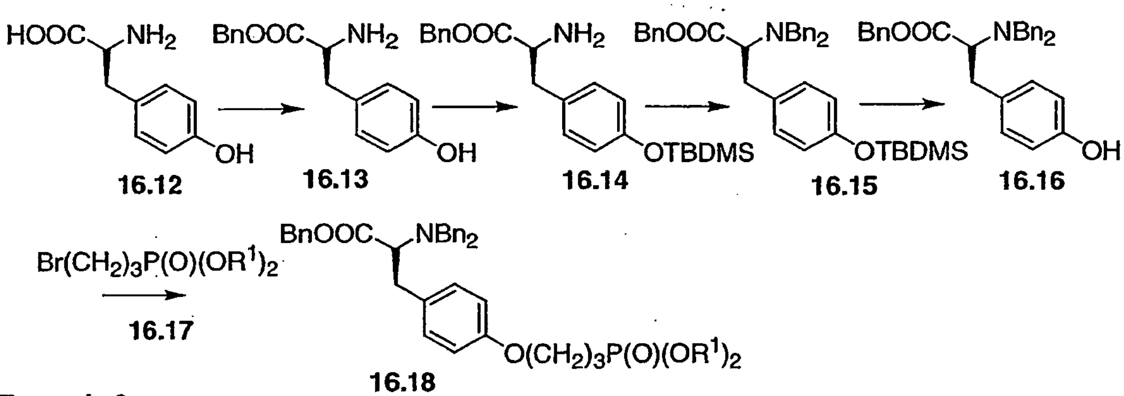
Using the above procedures, but employing, in place of 3-bromophenylalanine **18.5**, different bromophenylalanines b18.1, and/or different dialkylphosphites **18.3**, the corresponding products **18.4** are obtained.

Scheme 16

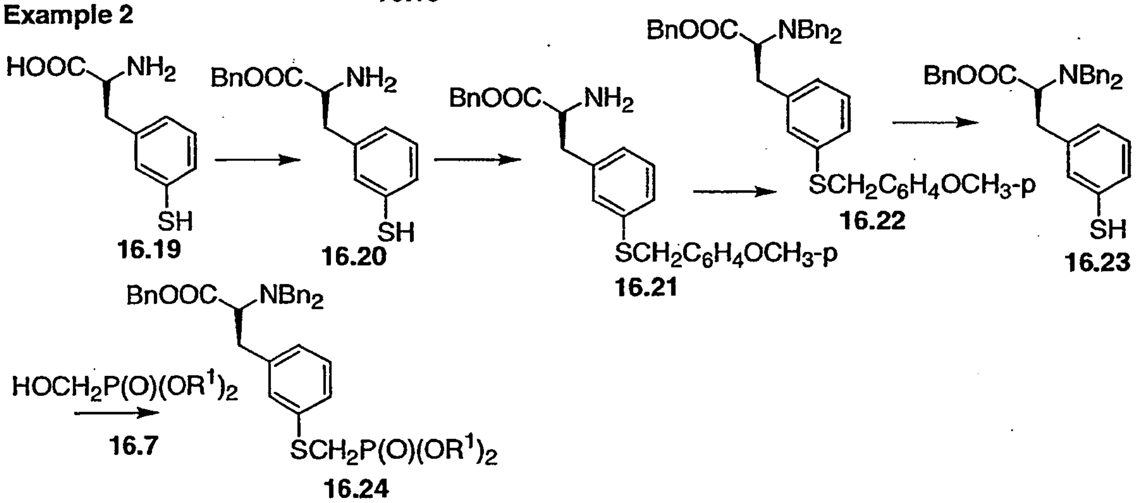
Method



Example1



Example 2



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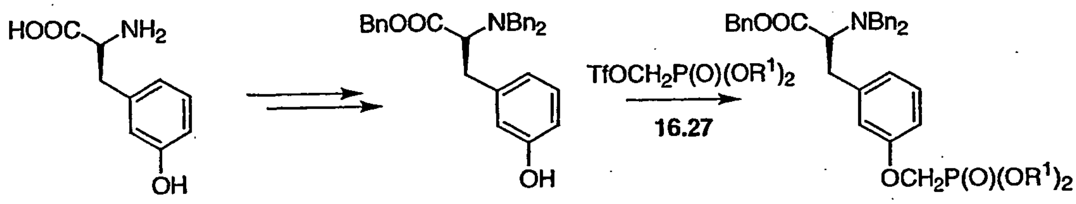
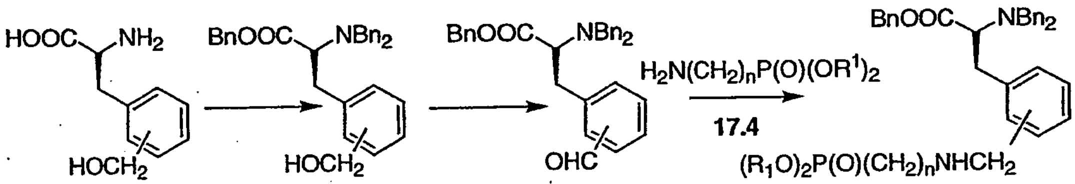
Example 3



16.25 16.26 16.28

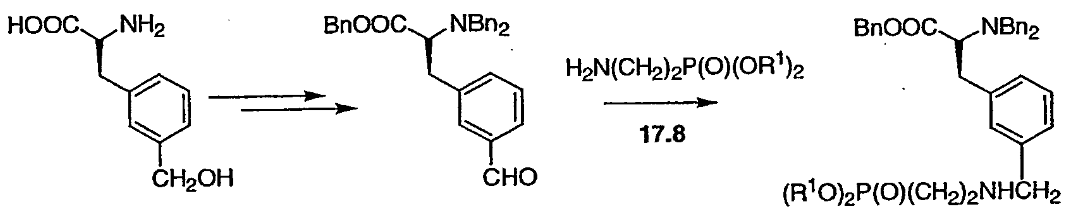
Scheme 17

Method



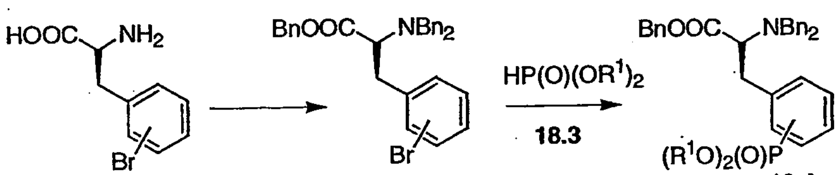
17.1 17.2 17.3 17.5

Example



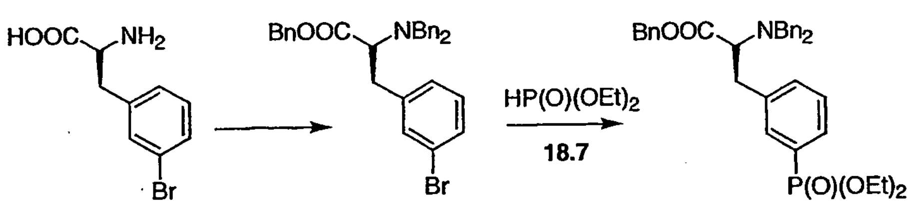
17.6 17.7 17.9

Scheme 18



18.1 18.2 18.4

Example



18.5 18.6 18.8

Preparation of phosphonate esters with structure 3.

Scheme **19** illustrates the preparation of compounds **3** in which the phosphonate ester moiety is attached directly to the phenyl ring. In this procedure, the ketonitrile **7.1**, prepared as described in J. Org. Chem., 1994, 59, 4080, is reacted with a bromobenzylmagnesium halide reagent **19.1**. The resultant ketoenamine **19.2** is then converted into the diacylated bromophenyl carbinol **19.3**. The conditions required for the conversion of the ketoenamine **19.2** into the carbinol **19.3** are similar to those described above (Scheme **4**) for the conversion of the ketoenamine **4.5** into the carbinol **4.12**. The product **19.3** is then reacted with a dialkyl phosphite **18.3**, in the presence of a palladium (0) catalyst, to yield the phosphonate ester **19.4**. The conditions for the coupling reaction are the same as those described above (Scheme **18**) for the preparation of the phosphonate ester **18.4**.

For example, the ketonitrile **7.1** is reacted, in tetrahydrofuran solution at -40°C, with three molar equivalents of 4-bromobenzylmagnesium bromide **19.5**, the preparation of which is described in Tetrahedron, 2000, 56, 10067, to afford the ketoenamine **19.6**. The latter compound is then converted into the bromophenyl carbinol **19.7**, using the sequence of reactions described above (Scheme 4) for the conversion of the ketoenamine **4.5** into the carbinol **4.12**. The resultant bromo compound **19.7** is then reacted with diethyl phosphite **18.3** and triethylamine, in toluene solution at reflux, in the presence of tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to afford the phosphonate product **19.8**.

Using the above procedures, but employing, in place of 4-bromobenzylmagnesium bromide **19.5**, different bromobenzylmagnesium halides **19.1** and/or different dialkyl phosphites **18.3**, there are obtained the corresponding phosphonate esters **19.4**.

Scheme **20** illustrates the preparation of compounds **3** in which the phosphonate ester moiety is attached to the nucleus by means of a phenyl ring. In this procedure, a bromophenyl-substituted benzylmagnesium bromide **20.1**, prepared from the corresponding bromomethyl compound by reaction with magnesium, is reacted with the ketonitrile **7.1**. The conditions for this transformation are the same as those described above (Scheme 4). The product of the Grignard addition reaction is then transformed, using the sequence of reactions described

above, (Scheme **4**) into the diacylated carbinol **20.2**. The latter compound is then coupled, in the presence of a palladium(0) catalyst, with a dialkyl phosphite **18.3**, to afford the phenylphosphonate **20.3**. The procedure for the coupling reaction is the same as those described above for the preparation of the phosphonate **19.8**.

For example, 4-(4-bromophenyl)benzyl bromide, prepared as described in DE 2262340, is reacted with magnesium to afford 4-(4-bromophenyl)benzylmagnesium bromine **20.4**. This product is then reacted with the ketonitrile **7.1**, as described above, to yield, after the sequence of reactions shown in Scheme **4**, the diacylated carbinol **20.5**. The latter compounds then reacted, as described above, (Scheme **18**) with a dialkyl phosphite **18.3**, to afford the phenylphosphonate **20.6**.

Using the above procedures, but employing, in place of 4-(4-bromophenyl)benzyl bromide **20.4**, different bromophenylbenzyl bromides **20.1**, and/or different dialkyl phosphites **18.3**, the corresponding products **20.3** are obtained.

Scheme **21** depicts the preparation of phosphonate esters **3** in which the phosphonate group is attached by means of a heteroatom and a methylene group. In this procedure, a hetero-substituted benzyl alcohol **21.1** is protected, affording the derivative **21.2**. The protection of phenyl hydroxyl, thiol and amino groups are described, respectively, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 277, 309. For example, hydroxyl and thiol substituents can be protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the phenol or thiophenol with a chlorotrialkylsilane, for example as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 68-86. Alternatively, thiol substituents can be protected by conversion to tert-butyl or adamantyl thioethers, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 289. Amino groups can be protected, for example by dibenzylation. The conversion of amines into dibenzylamines, for example by treatment with benzyl bromide in a polar solvent such as acetonitrile or aqueous ethanol, in the presence of a base such as triethylamine or sodium carbonate, is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G. M Wuts, Wiley, Second Edition 1990, p. 364. The resultant protected benzyl alcohol **21.1** is converted into a halo derivative **21.2**, in which Ha is chloro or bromo. The conversion of alcohols into chlorides and bromides is described, for example, in

Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 354ff and p. 356ff. For example, benzyl alcohols **21.2** can be transformed into the chloro compounds **21.3**, in which Ha is chloro, by reaction with triphenylphosphine and N-chlorosuccinimide, as described in J. Am. Chem. Soc., 106, 3286, 1984. Benzyl alcohols can be transformed into bromo compounds by reaction with carbon tetrabromide and triphenylphosphine, as described in J. Am. Chem. Soc., 92, 2139, 1970. The resultant protected benzyl halide **21.3** is then converted into the corresponding benzylmagnesium halide **21.4** by reaction with magnesium metal in an ethereal solvent, or by a Grignard exchange reaction treatment with an alkyl magnesium halide. The resultant substituted benzylmagnesium halide **21.4** is then converted, using the sequence of reactions described above (Scheme **4**) for the preparation of the diacylated carbinol **4.11**, into the carbinol **21.5** in which the substituent XH is suitably protected.

The protecting group is then removed to afford the phenol, thiophenol or amine **21.6**. Deprotection of phenols, thiophenols and amines is described respectively in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990. For example, trialkylsilyl ethers or thioethers can be deprotected by treatment with a tetraalkylammonium fluoride in an inert solvent such as tetrahydrofuran, as described in J. Am Chem. Soc., 94, 6190, 1972. Tert-butyl or adamantyl thioethers can be converted into the corresponding thiols by treatment with mercuric trifluoroacetate in aqueous acetic acid at ambient temperatures, as described in Chem. Pharm. Bull., 26, 1576, 1978. N,N-dibenzyl amines can be converted into the unprotected amines by catalytic reduction in the presence of a palladium catalyst, as described above (Scheme **1**). The resultant phenol, thiophenol or amine **21.6** is then converted into the phosphonate ester **21.7** by reaction with an activated derivative of a dialkyl hydroxymethyl phosphonate **16.27**, in which Lv is a leaving group. The reaction is conducted under the same conditions as described above for the conversion of **16.5** to **16.11** (Scheme **16**).

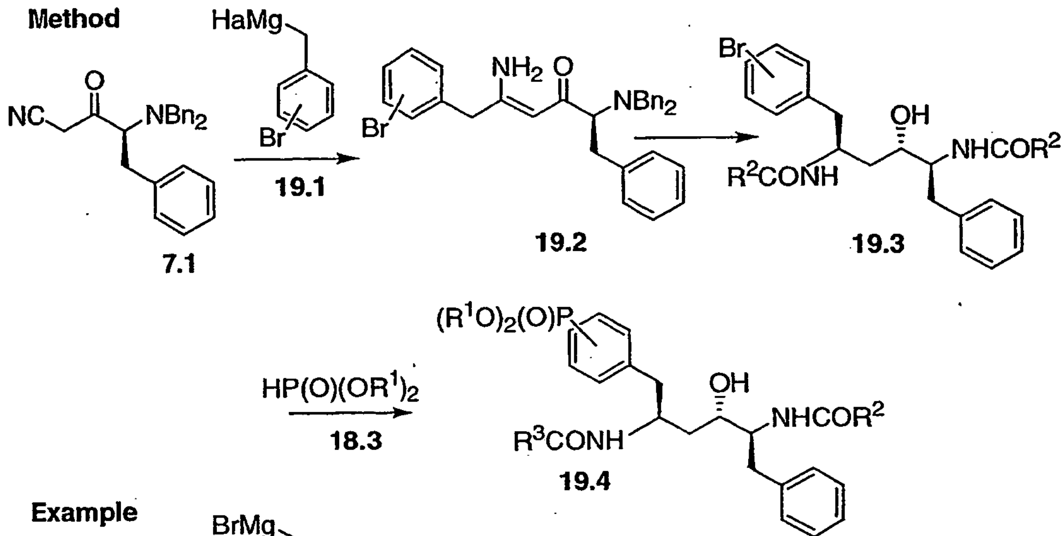
For example, 3-hydroxybenzyl alcohol **21.8** (Aldrich) is reacted with chlorotriisopropylsilane and imidazole in dimethylformamide, as described in Tet. Lett., 2865, 1964, to afford the silyl ether **21.9**. This compound is reacted with carbon tetrabromide and triphenylphosphine in dichloromethane, as described in J. Am. Chem. Soc., 109, 2738, 1987, to afford the brominated product **21.10**. This material is reacted with magnesium in ether to afford the Grignard reagent **21.11**, which is then subjected to the series of reaction shown in Scheme **4** to

afford the carbinol **21.12**. The triisopropylsilyl protecting group is then removed by treatment of the ether **21.12** with tetrabutylammonium fluoride in tetrahydrofuran, as described in J. Org. Chem., 51, 4941, 1986. The resultant phenol **21.13** is then reacted with a dialkyl trifluoromethanesulfonyloxymethylphosphonate **16.27**, prepared as described in Tet. Lett., 1986, 27, 1477, in dimethylformamide solution at 60°C in the presence of cesium carbonate, to afford the phosphonate product **21.14**.

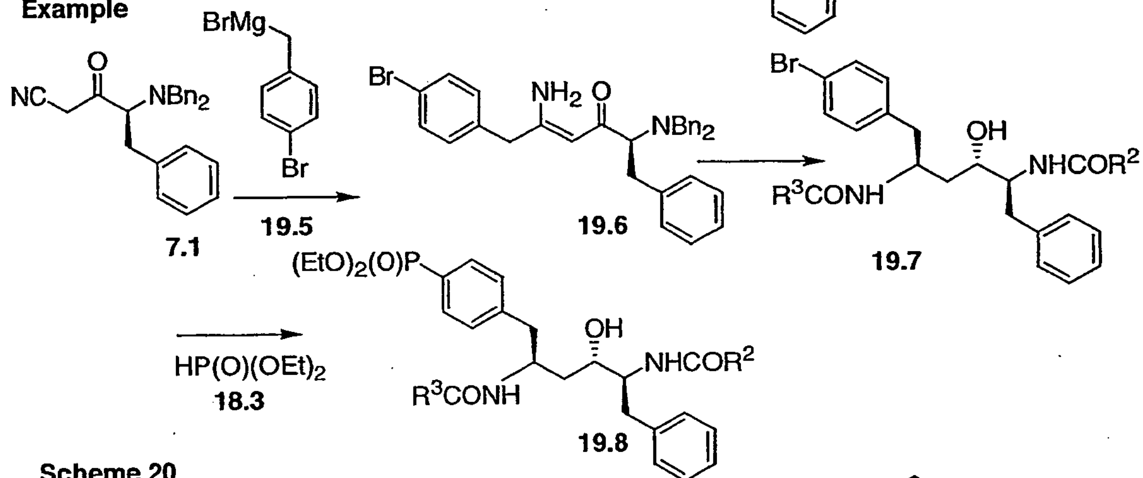
Using the above procedures, but employing, in place of 3-hydroxybenzyl alcohol **21.8**, different hydroxy, mercapto or amino-substituted benzyl alcohols **21.1**, and/or different dialkyl trifluoromethanesulfonyloxymethyl phosphonates **16.27**, the corresponding products **21.7** are obtained.

Scheme 19

Method

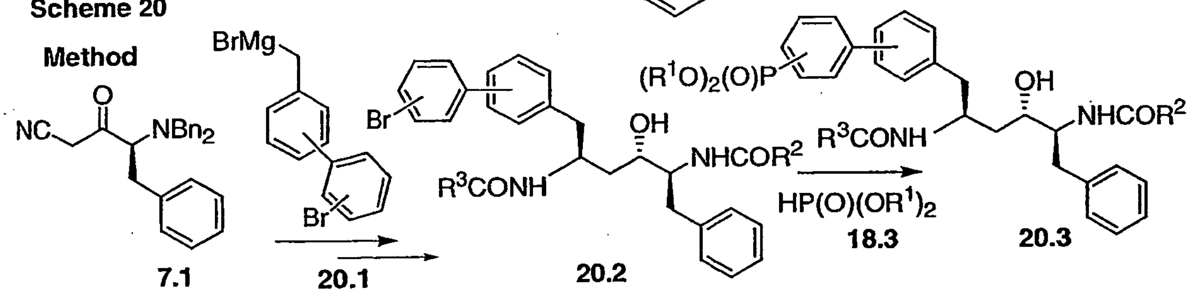


Example

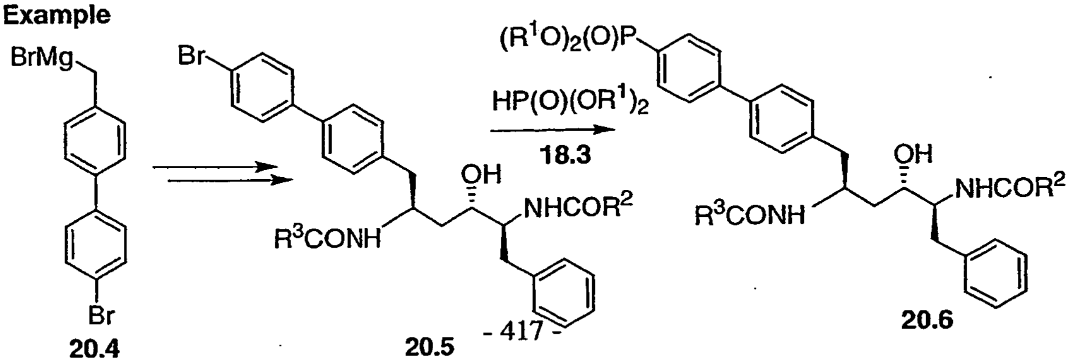


Scheme 20

Method

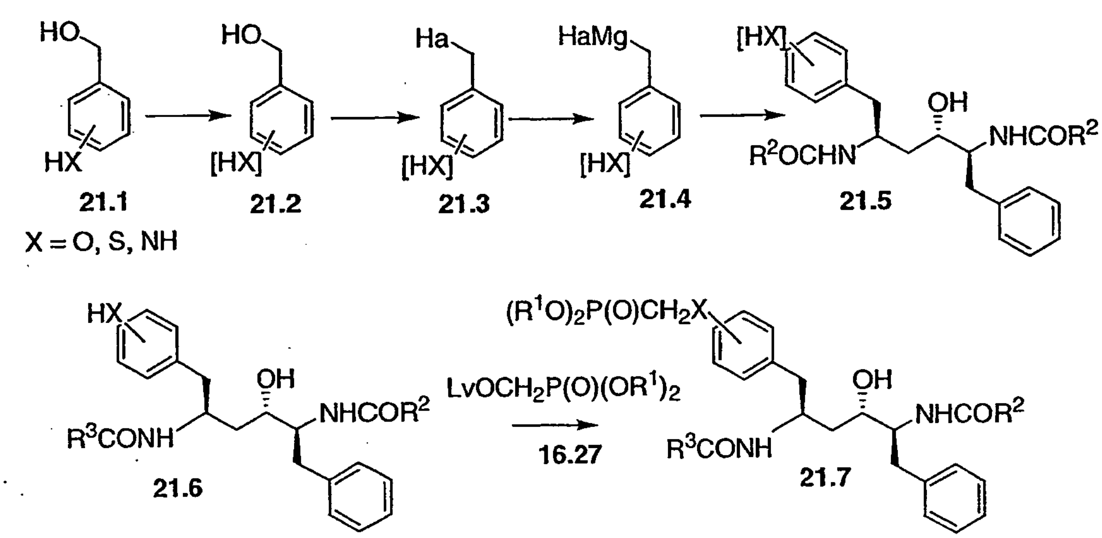


Example

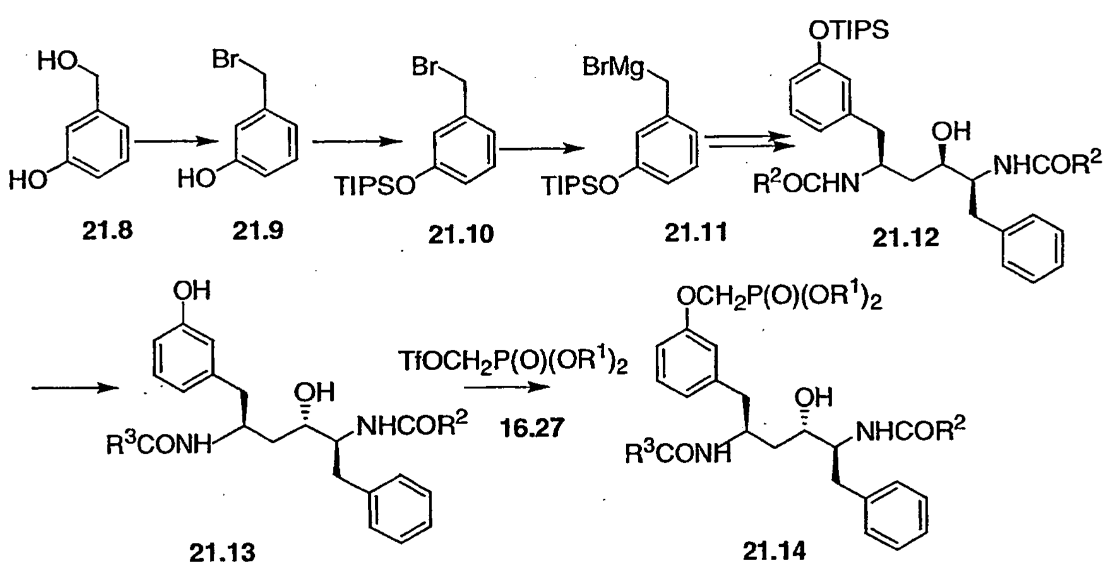


Scheme 21

Method



Example



Preparation of phosphonate-containing carboxylic acids 1.5.

Scheme **22** illustrates methods for the preparation of carboxylic acids **1.5**, in which A is Br, and methods for the conversion of the bromo substituent into various phosphonate-containing substituents.

In this procedure, 3-bromo-2-methylpropanamide **22.1** is substituted for the isobutyramide derivative **13.1** in the reaction sequence illustrated in Scheme **13**, so as to afford 2-{3-[2-(2-bromo-1-methyl-ethyl)-thiazol-4-ylmethyl]-3-methyl-ureido}-3-methyl-butyric acid methyl ester, **22.2**. The conditions required for the various reactions are the same as those described above (Scheme**13**). The bromo-substituted ester **22.2** is then subjected to various transformations so as to introduce phosphonate-containing substituents. For example, the ester **22.2** is reacted with a trialkyl phosphate **22.3** in an Arbuzov reaction, to afford the phosphonate ester **22.4**. The preparation of phosphonates by means of the Arbuzov reaction is described, for example, in Handb. Organophosphorus Chem., 1992, 115. The reaction is performed by heating the substrate at 100°C to 150°C with an excess of the trialkyl phosphite. The methyl ester group in the phosphonate product **22.4** is then hydrolyzed, using the procedures described above, (Scheme **13**) to prepare the carboxylic acid **22.5**.

For example, as shown in Scheme **22**, Example 1, the bromo compound **22.2** is heated at 120°C with a ten molar excess of tribenzyl phosphite **22.6** to afford the benzylphosphonate **22.7**. Hydrolysis of the methyl ester, as described above, then yields 2-(3-{2-[2-(bis-benzyloxy-phosphoryl)-1-methyl-ethyl]-thiazol-4-ylmethyl}-3-methyl-ureido)-3-methyl-butyric acid **22.8.**

Alternatively, the bromoester **22.2** is oxidized to the corresponding aldehyde **22.9**. Methods for the oxidation of bromo compounds to the corresponding aldehyde are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989 p. 599. The transformation can be effected by reaction of the aldehyde with dimethyl sulfoxide, optionally in the presence of a silver salt, as described in Chem. Rev., 67, 247, 1967. Alternatively, the bromo compound is reacted with trimethylamine oxide, as described in Ber., 94, 1360, 1961, to prepare 3-methyl-2-{3-methyl-3-[2-(1-methyl-2-oxo-ethyl)-thiazol-4-ylmethyl]-ureido}-butyric-acid methyl ester **22.9**. The aldehyde is then reacted with a dialkyl aminoalkyl phosphonate **22.10** in a reductive amination reaction to afford the

aminophosphonate **22.11**. The conditions for the reductive amination reaction are the same as those described above for the preparation of the aminophosphonate **17.5**, (Scheme **17**). The methyl ester group present in the product **22.11** is then hydrolyzed, as described above, to yield the carboxylic acid **22.12**.

For example, as shown in Scheme **22**, Example 2, the bromo compound **22.2** is heated at 80°C in dimethylsulfoxide solution, in the presence of one molar equivalent of silver tetrafluoborate and triethylamine, as described in J. Chem. Soc., Chem. Comm., 1338, 1970, to afford the aldehyde **22.9**. Reductive amination of the product, in the presence of a dialkyl aminoethyl phosphonate **22.13**, the preparation of which is described in J. Org. Chem., 2000, 65, 676 and sodium triacetoxy borohydride, then affords the amino phosphonate **22.14**. Hydrolysis of the methyl ester, as described above, then afford the carboxylic acid **22.15**.

Alternatively, the bromo compound **22.2** is reacted with a dialkyl thioalkyl phosphonate **22.16** to effect displacement of the bromo substituent to afford the thioether **22.17**. The preparation of thioethers by the reaction of bromo compounds with thiols is described, for example, in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 787. The reactants are combined in the presence of a suitable base, such as sodium hydroxide, dimethylaminopyridine, potassium carbonate and the like, in a polar organic solvent such as dimethylformamide or ethanol, to afford the thioether **22.17**. The product is then subjected to hydrolysis, as described above, to afford the carboxylic acid **22.18**.

For example, as shown in Scheme **22**, Example 3, the bromo compound **22.2** is reacted with a dialkyl thioethylphosphonate **22.19**, the preparation of which is described in Aust. J. Chem., 43, 1123, 1990, and dimethylaminopyridine, in dimethylformamide solution at ambient temperature, to yield the thioether **22.20**. Hydrolysis of the methyl ester group, as described above, then afford the carboxylic acid **22.21**.

Scheme **23** illustrates the preparation of carboxylic acids **23.7** in which the phosphonate moiety is attached to the isopropyl group by means of a phenyl ring and a heteroatom. In this procedure, the hydroxy or mercapto substituent on a phenylbutanamide **23.1** is protected. Methods for the protection of hydroxyl and thiol groups are described above (Scheme **21**). The protected amide **23.2** is then subjected to the series of reactions illustrated in Scheme **13**, so as to afford the O- or S-protected ester **23.3**. The protecting group is then removed. Methods for the deprotection of phenols and thiophenols are described above (Scheme **16**).

The resultant phenol or thiophenol **23.4** is then reacted with a dialkyl bromoalkyl phosphonate **23.5**, to afford the ether or thioether compounds **23.6**. Conditions for the alkylation of phenols and thiophenols are described above (Scheme **16**). The ester groups present in the product **23.6** is then hydrolyzed, as described above, to afford the corresponding carboxylic acid **23.7**.

For example, 3-(4-hydroxyphenyl)butyric acid **23.8**, prepared as described in J. Med. Chem., 1992, 35, 548, is converted into the acid chloride by reaction with thionyl chloride. The acid chloride is then reacted with excess aqueous ethanolic ammonia to afford the amide **23.9**. This compound is converted into the tert. butyldimethylsilyl derivative **23.10** by treatment with tert-butylchlorodimethylsilane and imidazole in dichloromethane. The resultant amide **23.10** is then subjected to the series of reactions shown in Scheme **13**, so as to yield the ester **23.11**. Desilylation, by treatment with tetrabutylammonium fluoride in tetrahydrofuran, then affords the phenol **23.12**. This compound is reacted with a dialkyl bromoethyl phosphonate **23.13** (Aldrich) and potassium carbonate, in dimethylformamide at 80°C, to produce the ether **23.14**. Hydrolysis of the ester group, by treatment with aqueous methanolic lithium hydroxide, then affords the carboxylic acid **23.15**.

Using the above procedures, but employing, in place of the amide **23.9**, different hydroxy- or thio-substituted amides **23.23.1**, and/or different bromoalkylphosphonates **23.5**, the corresponding products **23.7** are obtained.

Scheme **24** and **25** describes the preparation of carboxylic acids **9.1** in which the phosphonate moiety is attached to the amine component. In this procedure, the chloromethylthiazole **14.1**, is reacted with a dialkyl aminoalkyl phosphonate **24.1** to produce the substituted amine **24.2**. The preparation of amines by reacting amines with alkyl halides is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 397. Typically, the components are reacted together in a polar solvent such as an alkanol or dimethylformamide and the like, to yield the substituted amine **24.2**. The latter compound is then converted into the carboxylic acid **24.3**, by means of the series of reactions shown in Scheme **14**.

For example, the chloromethyl thiazole **14.1** is reacted at 50°C in acetonitrile solution containing potassium carbonate, with one molar equivalent of a dialkyl aminomethyl phosphonate **24.4**, prepared as described in Bioorg. Chem., 2001, 29, 77, to afford the

substituted amine **24.5**. The product is then converted, using the reactions shown in Scheme **14**, into the carboxylic acid **24.6**.

Using the above procedures, but employing, in place of the dialkyl aminoethyl phosphonate **24.4**, different dialkyl aminoalkyl phosphonates **24.1**, the corresponding products **24.3** are obtained.

Scheme **25** illustrates the preparation of carboxylic acids **9.1** in which the phosphonate moiety is attached to the amine component by means of a saturated or unsaturated alkyl chain and a phenyl ring. In this procedure, the chloromethylthiazole **14.1** is reacted with allylamine **25.1**, using the procedures described above (Scheme **24**) to afford allyl-(2-isopropyl-thiazol-4-ylmethyl)-amine **25.2**. The ester amine is then converted, by means of the series of reactions shown in Scheme **14**, into 2-[3-allyl-3-(2-isopropyl-thiazol-4-ylmethyl)-ureido]-3-methyl-butyric acid methyl ester **25.3**. This material is coupled with a dialkyl bromo-substituted phenylphosphonate **25.4**, under the conditions of the palladium-catalyzed Heck reaction, to afford the coupled product **25.5**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Hydrolysis of the methyl ester, as described above, then yields the carboxylic acid **25.6**. Optionally, the double bond present in the product **25.6** is reduced to afford the dihydro analog **25.7**. The double bond is reduced in the presence of a palladium catalyst, such as, for example, 5% palladium on carbon, in a solvent such as methanol or ethanol, to afford the product **25.7**.

For example, the allyl-substituted urea **25.3** is reacted with a dialkyl 4-bromophenyl phosphonate **25.8**, prepared as described in J. Chem. Soc., Perkin Trans.,1977, 2, 789 in the presence of tetrakis(triphenylphosphine)palladium (0) and triethylamine, to afford the phosphonate ester **25.9**. Ester hydrolysis, as described above, then affords the carboxylic acid **25.10**. Hydrogenation, as described above, then affords the saturated analog **25.11**.

Using the above procedures, but employing, in place of the 4-bromophenyl phosphonate **25.8**, different bromophenyl phosphonates **25.4**, the corresponding products **25.6** and **25.7** are obtained.

Scheme **26** illustrates the preparation of carboxylic acids **11.1** in which the phosphonate moiety is attached to the valine substructure. In this procedure, 2-amino-4-bromo-3-methyl-butyric acid methyl ester **26.1**, prepared as described in U.S. Patent 5,346,898, is reacted with a chloroformate, for example 4-nitrophenyl chloroformate, to prepare the activated derivative **26.2** in which X is a leaving group. For example, the aminoester **26.1** is reacted with 4-nitrophenylchloroformate in dichloromethane at 0°C, as described in U.S. 5,484,801, to afford the product **26.2** in which X is 4-nitrophenoxy. The latter compound is reacted with (2-isopropyl-thiazol-4-ylmethyl)-methyl-amine **26.3**, prepared as described in U.S. 5,484,801, in the presence of a base such as triethylamine or dimethylaminopyridine, in an inert solvent such as dichloromethane or tetrahydrofuran, to afford 4-bromo-2-[3-(2-isopropyl-thiazol-4-ylmethyl)-3-methyl-ureido]-3-methyl-butyric acid methyl ester **26.4**. The bromo compound **26.4** is then oxidized to afford the aldehyde **26.5**. The oxidation of bromo compounds to afford the corresponding aldehydes is described above (Scheme 22). In a typical procedure, the bromo compound is heated at 80°C in dimethylsulfoxide solution, optionally in the presence of silver salt such as silver perchlorate or silver tetrafluoborate, as described in J. Am. Chem. Soc., 81, 4113, 1959, to afford 2-[3-(2-isopropyl-thiazol-4-ylmethyl)-3-methyl-ureido]-3-methyl-4-oxo-butyric acid methyl ester **26.5**. The aldehyde is then subjected to a reductive amination procedure, in the presence of a dialkyl aminoalkyl phosphonate **26.6**, to afford the amine product **26.7**. The preparation of amines by means of reductive alkylation reactions is described above (Scheme **22**). Equimolar amounts of the aldehyde **26.5** and the amine **26.6** are reacted in the presence of a boron-containing reducing agent such as, for example, sodium triacetoxyborohydride, to yield the amine **26.7**. The methyl ester is then hydrolyzed, as described above, to yield the carboxylic acid **26.8**.

For example, 2-[3-(2-isopropyl-thiazol-4-ylmethyl)-3-methyl-ureido]-3-methyl-4-oxo-butyric acid methyl ester **26.5** is reacted with a dialkyl aminoethylphosphonate **26.9** and sodium cyanoborohydride, to afford the amine product **26.10**. The methyl ester is then hydrolyzed, as described above to yield the carboxylic acid **26.11**.

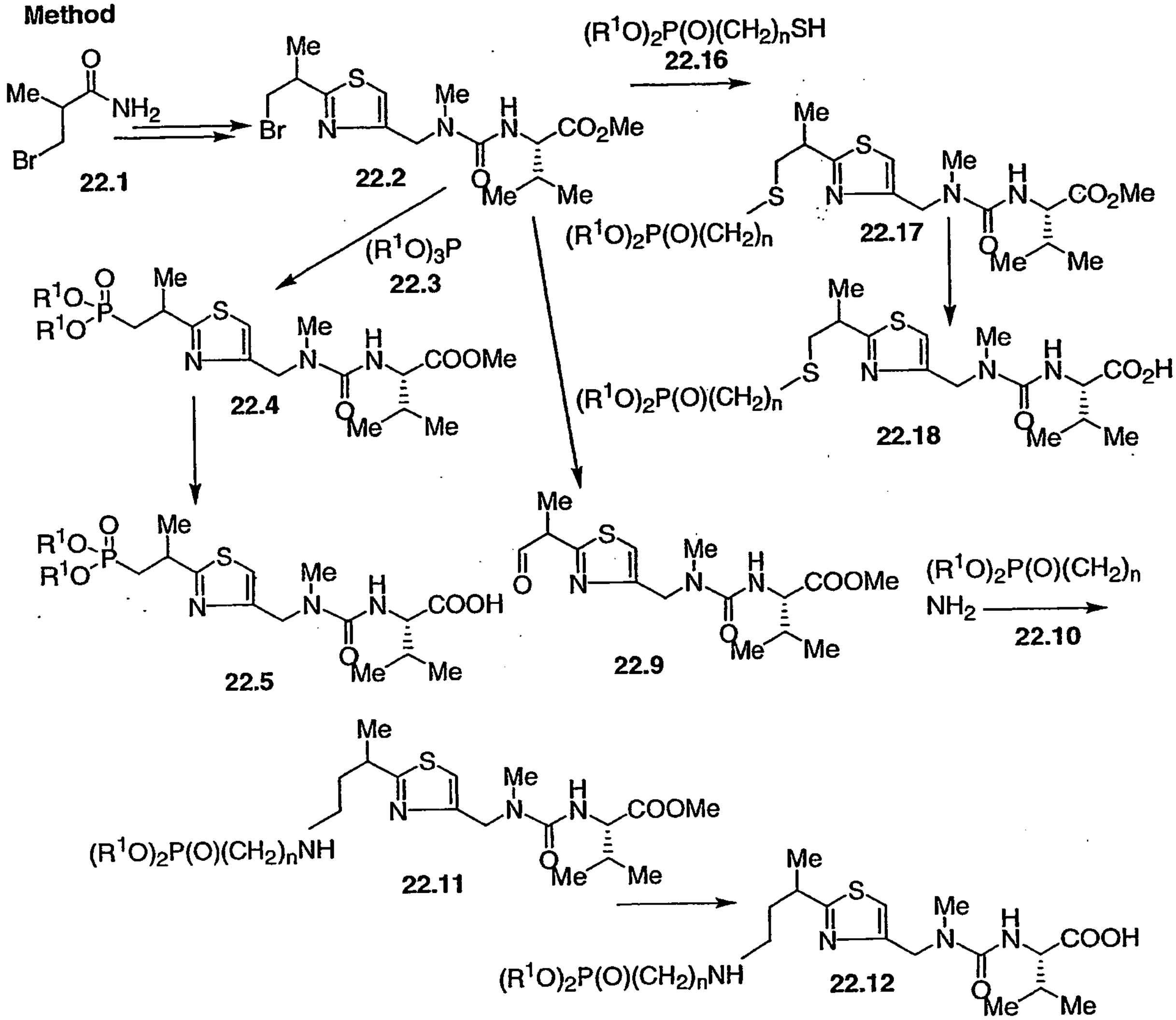
Using the above procedures, but employing, in place of the dialkyl aminoethylphosphonate **26.9**, different aminoalkyl phosphonates **26.6**, the corresponding products **26.8** are obtained. Alternatively, the bromo-substituted methyl ester **26.4** is then reacted with a dialkyl mercaptoalkyl phosphonate **26.12** to afford the thioether **26.13**. The preparation of thioethers by the reaction of bromo compounds with thiols is described, for example, in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 787. The reactants are combined in the presence of a suitable base, such as sodium hydroxide, dimethylamino pyridine, potassium or cesium carbonate and the like, in a polar organic solvent such as dimethylformamide or ethanol, to afford the thioether **26.13**. The methyl ester is then hydrolyzed, as described above to yield the carboxylic acid **26.14**.

For example, the bromo compound **26.4** is reacted with a dialkyl mercaptoethyl phosphonate **26.15**, the preparation of which is described in Aust. J. Chem., 43, 1123, 1990, in dimethylformamide solution, in the presence of cesium carbonate, to produce the thio ether product **26.16**. The methyl ester is then hydrolyzed, as described above, to yield the carboxylic acid **26.17**.

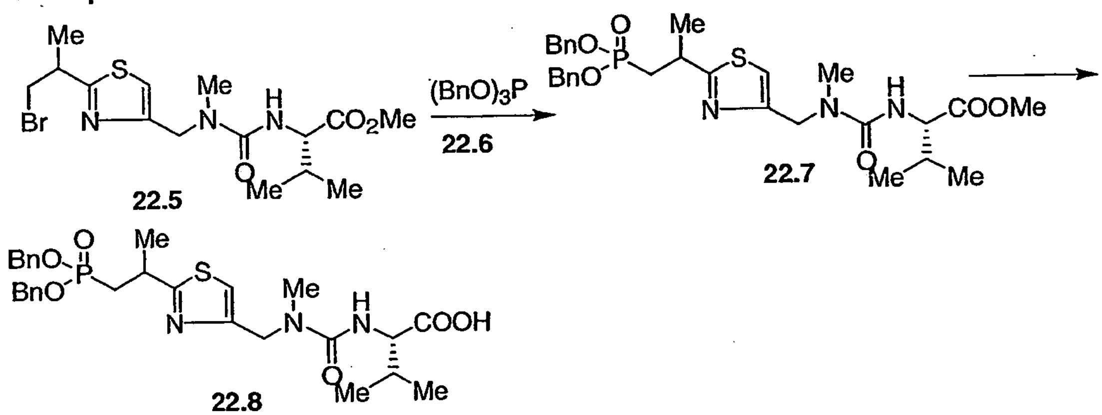
Using the above procedures, but employing, in place of the dialkyl mercaptoethyl phosphonate **26.15**, different mercaptoalkyl phosphonates **26.12**, the corresponding products **26.14** are obtained.

Scheme 22

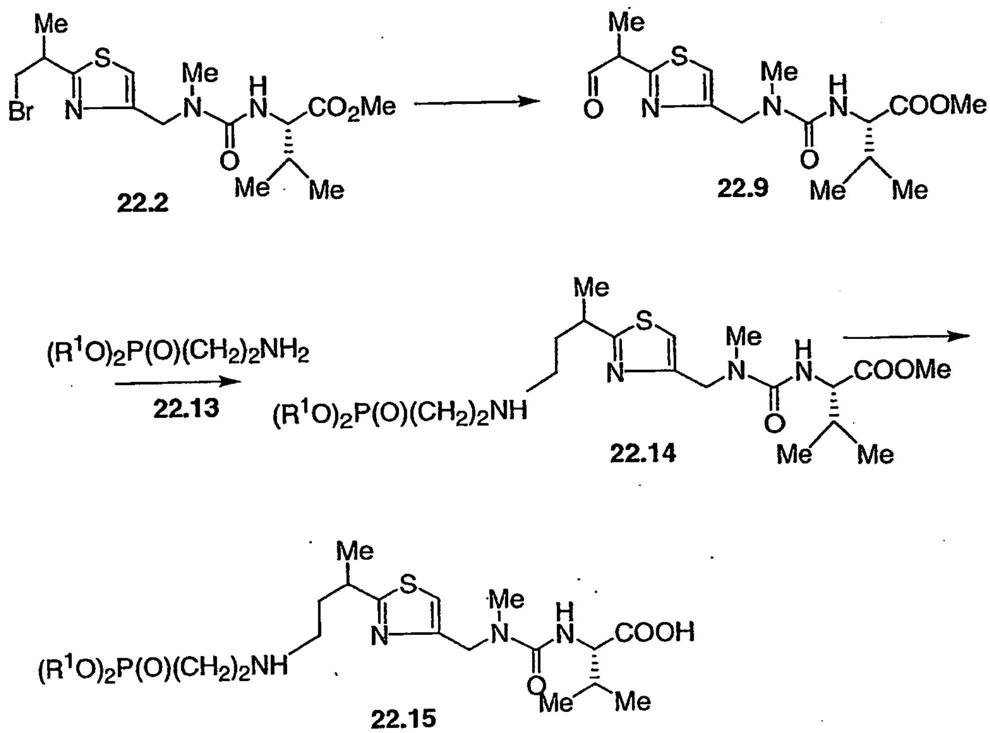
Method



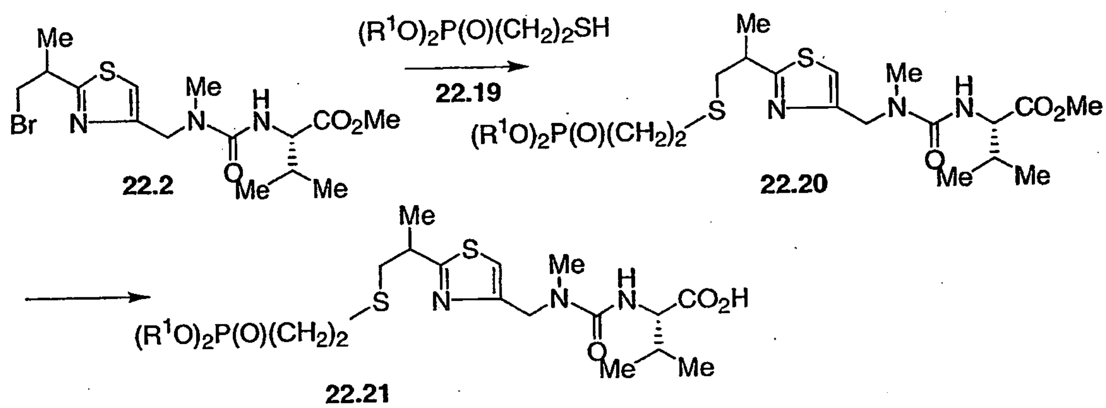
Example 1



Example 2

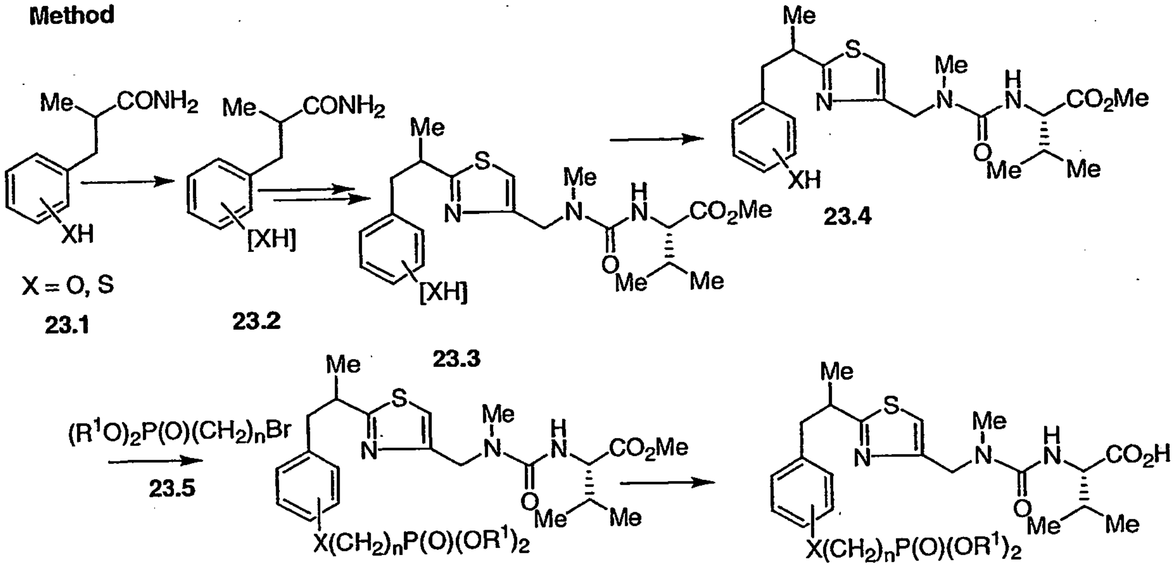


Example 3



Scheme 23

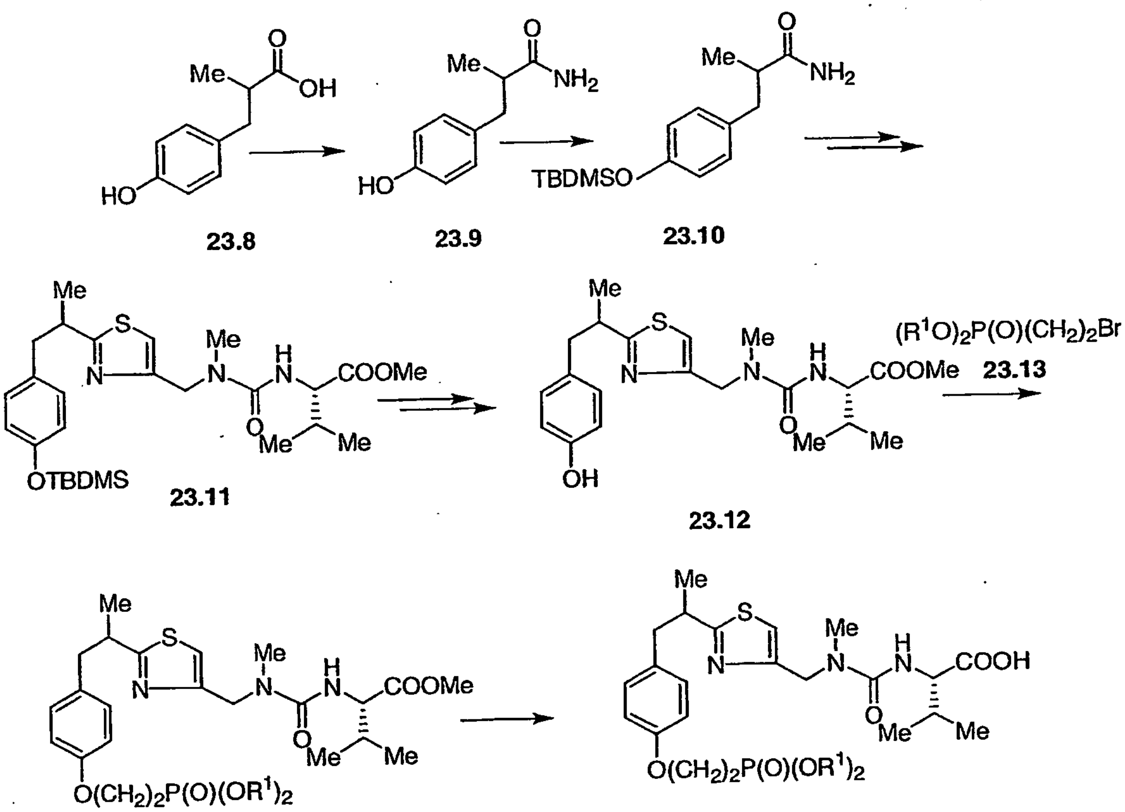
Method



X = O, S

23.1 23.2 23.3 23.4 23.5 23.6 23.7

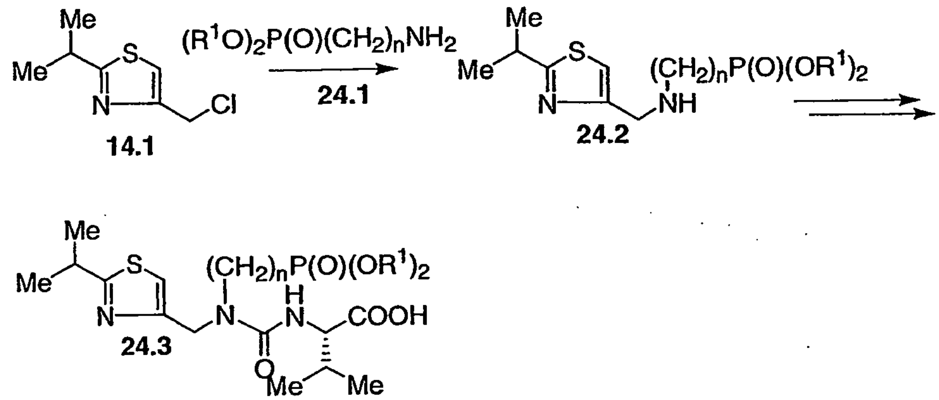
Example



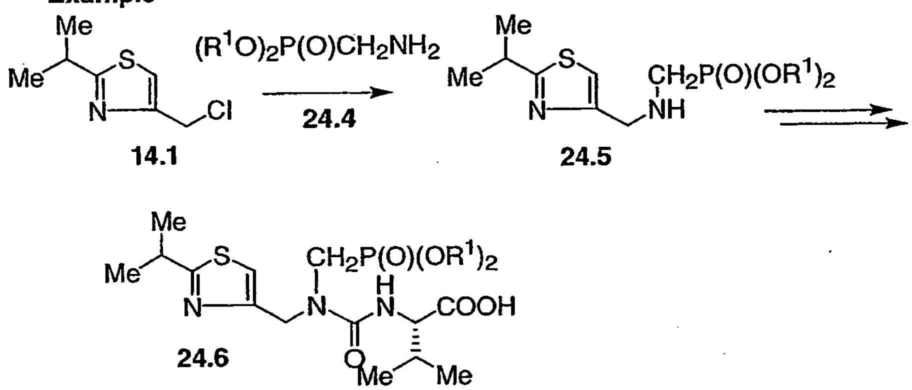
23.8 23.9 23.10 23.11 23.12 23.13 23.14 23.15

Scheme 24

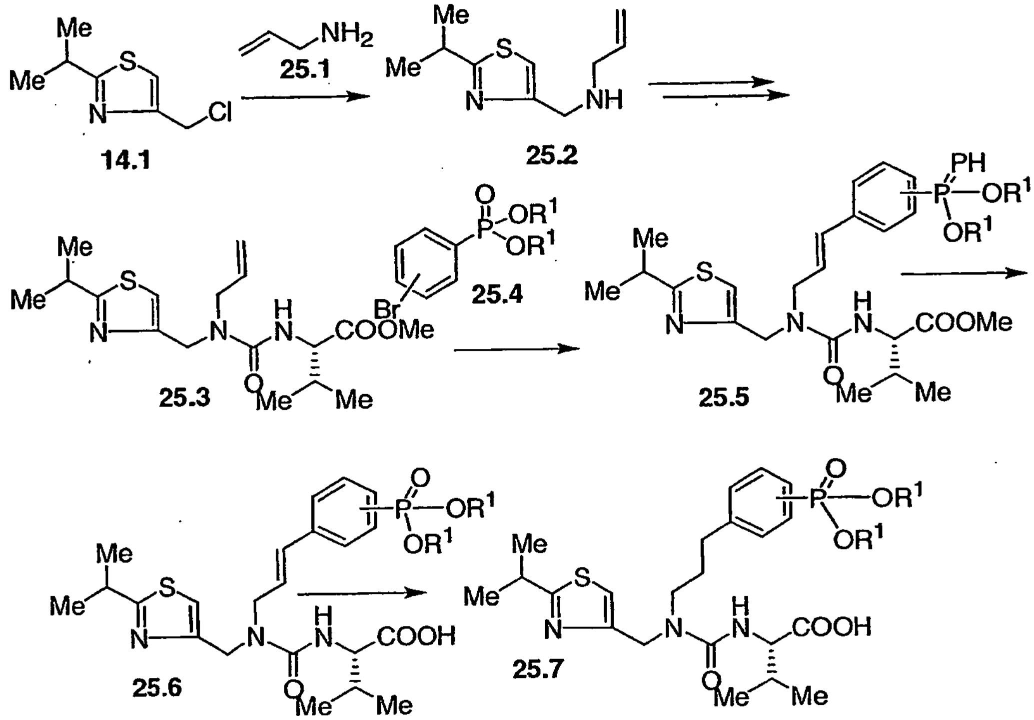
Method



Example

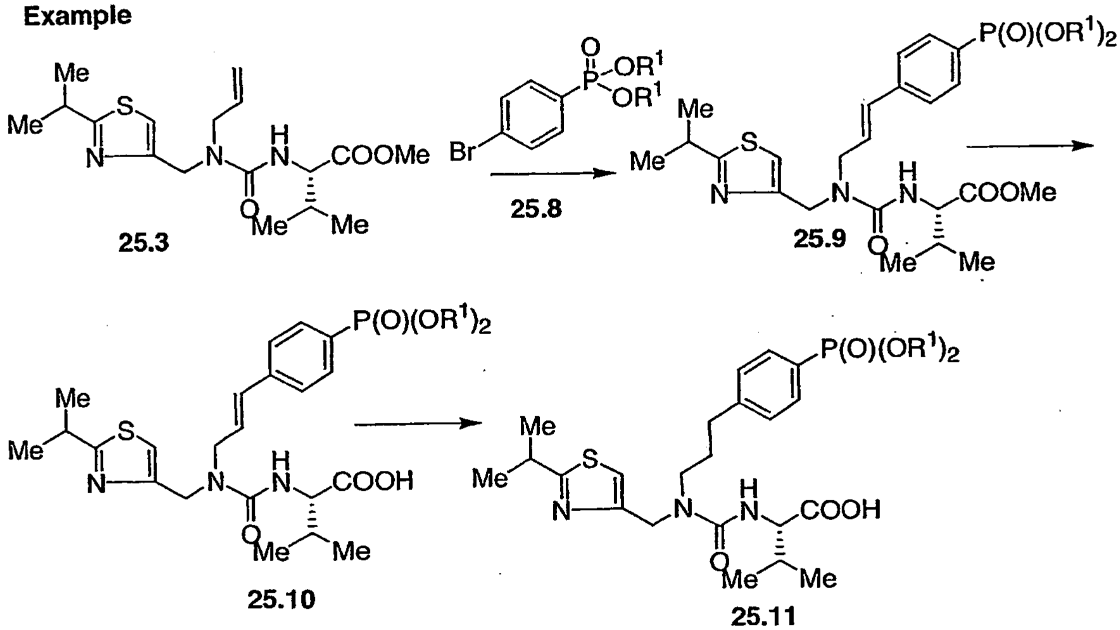


Scheme 25
Method



14.1 25.1 25.2 25.3 25.4 25.5 25.6 25.7

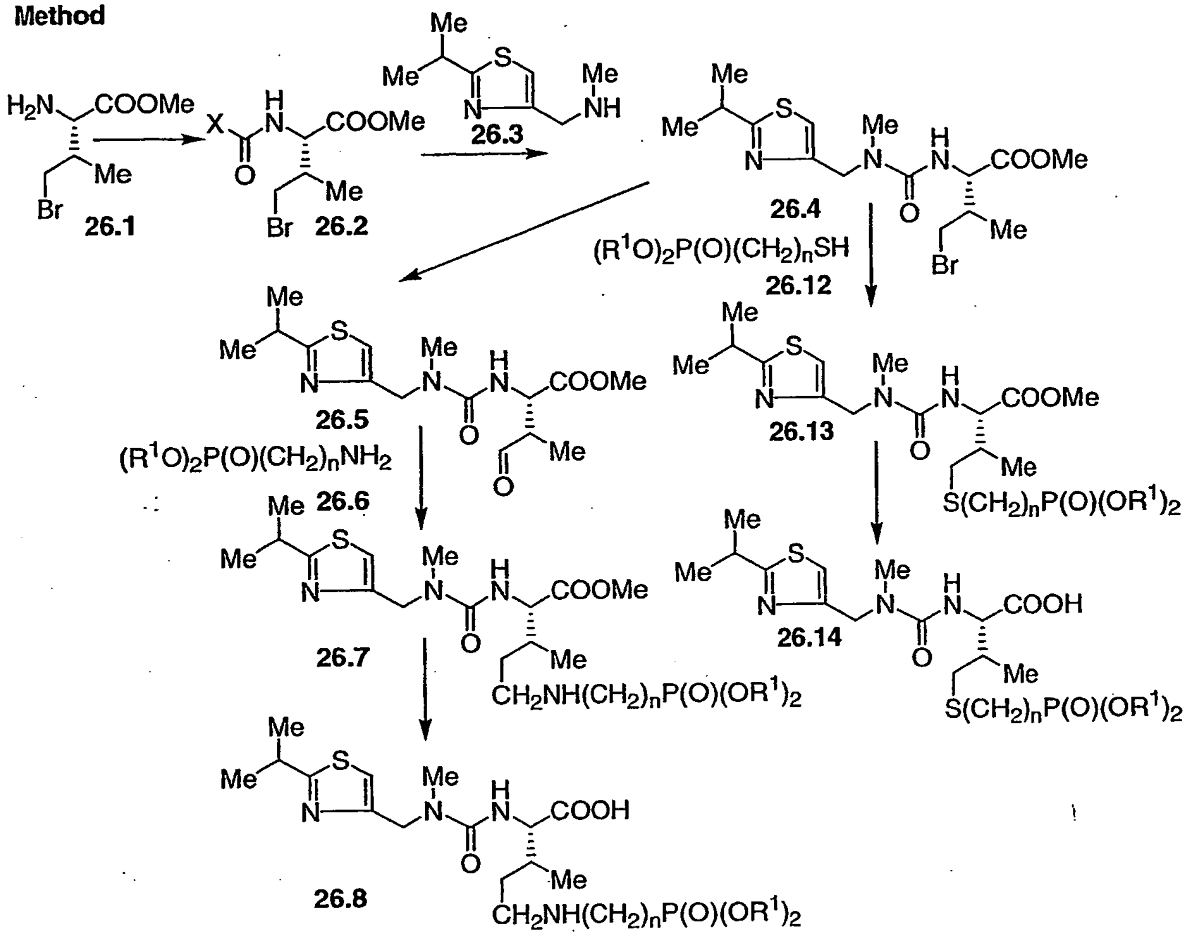
Example



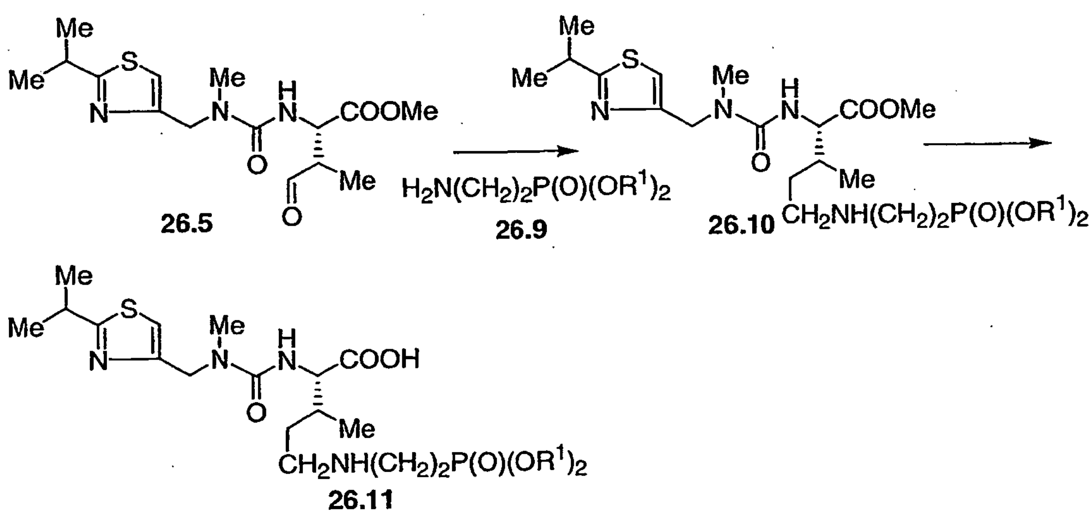
25.3 25.8 25.9 25.10 25.11

Scheme 26

Method



Example 1



Interconversions of the phosphonates R-link-P(O)(OR^1)$_2$, R-link-P(O)(OR^1)(OH) and R-link-P(O)(OH)$_2$.

Schemes **1-26** described the preparations of phosphonate esters of the general structure R-link-P(O)(OR^1)$_2$, in which the groups R^1, the structures of which are defined in Chart **1**, may be the same or different. The R^{1}groups attached to a phosphonate esters **1-7**, or to precursors thereto, may be changed using established chemical transformations. The interconversions reactions of phosphonates are illustrated in Scheme **27**. The group R in Scheme **27** represents the substructure to which the substituent link-P(O)(OR^1)$_2$ is attached, either in the compounds **1-7** or in precursors thereto. The R^1 group may be changed, using the procedures described below, either in the precursor compounds, or in the esters **1-7**. The methods employed for a given phosphonate transformation depend on the nature of the substituent R^1. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester **27.1** into the corresponding phosphonate monoester **27.2** (Scheme **27**, Reaction 1) can be accomplished by a number of methods. For example, the ester **27.1** in which R^{1}is an aralkyl group such as benzyl, can be converted into the monoester compound **27.2** by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in J. Org. Chem., 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°C. The conversion of the diester **27.1** in which R^{1}is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester **27.2** can be effected by treatment of the ester **27.1** with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran.
Phosphonate diesters **27.1** in which one of the groups R^{1}is aralkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters **27.2** in which R^{1}is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R^{1}are alkenyl, such as allyl, can be converted into the monoester **27.2** in which R^{1}is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by

using the procedure described in J. Org. Chem., 38 3224 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester **27.1** or a phosphonate monoester **27.2** into the corresponding phosphonic acid **27.3** (Scheme **27**, Reactions 2 and 3) can effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in J. Chem. Soc., Chem. Comm., 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester **27.2** in which $R^1$is aralkyl such as benzyl, can be converted into the corresponding phosphonic acid **27.3** by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate monoester **27.2** in which $R^1$is alkenyl such as, for example, allyl, can be converted into the phosphonic acid **27.3** by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in Helv. Chim. Acta., 68, 618, 1985. Palladium catalyzed hydrogenolysis of phosphonate esters **27.1** in which $R^1$is benzyl is described in J. Org. Chem., 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters **27.1** in which $R^1$is phenyl is described in J. Amer. Chem. Soc., 78, 2336, 1956.

The conversion of a phosphonate monoester **27.2** into a phosphonate diester **27.1** (Scheme **27**, Reaction 4) in which the newly introduced R^1group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl can be effected by a number of reactions in which the substrate **27.2** is reacted with a hydroxy compound R^1OH, in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester **27.2** to the diester **27.1** can be effected by the use of the Mitsonobu reaction, as described above (Scheme **16**). The substrate is reacted with the hydroxy compound R^1OH, in the presence of

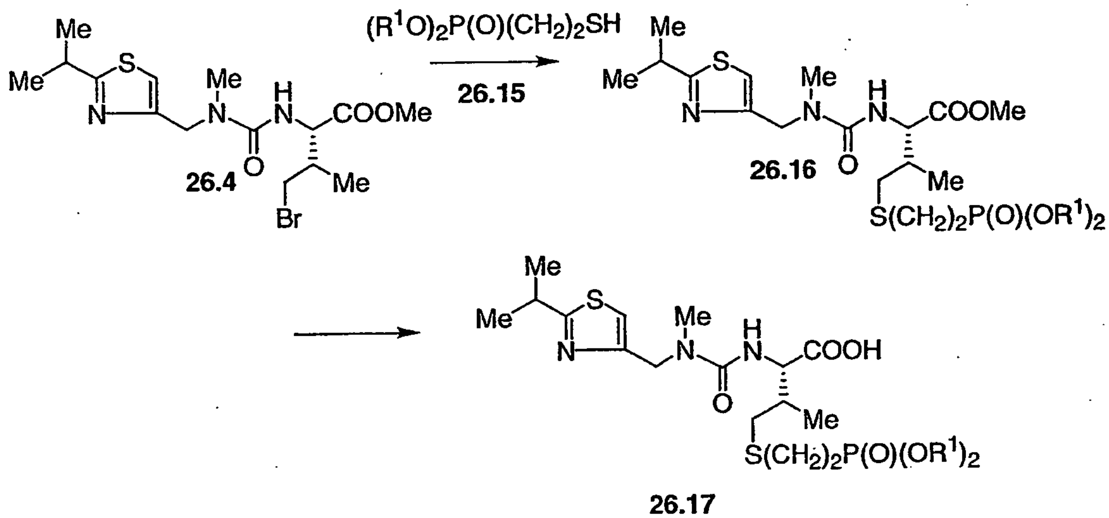
diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester **27.2** can be transformed into the phosphonate diester **27.1**, in which the introduced R^1 group is alkenyl or aralkyl, by reaction of the monoester with the halide R^1Br, in which R^1 is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the phosphonate diester in a two step procedure. In the first step, the phosphonate monoester **27.2** is transformed into the chloro analog $RP(O)(OR^1)Cl$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $RP(O)(OR^1)Cl$ is then reacted with the hydroxy compound R^1OH, in the presence of a base such as triethylamine, to afford the phosphonate diester **27.1**.

A phosphonic acid R-link-$P(O)(OH)_2$ can be transformed into a phosphonate monoester $RP(O)(OR^1)(OH)$ (Scheme **27**, Reaction 5) by means of the methods described above of for the preparation of the phosphonate diester R-link-$P(O)(OR^1)_2$ **27.1**, except that only one molar proportion of the component R^1OH or R^1Br is employed.

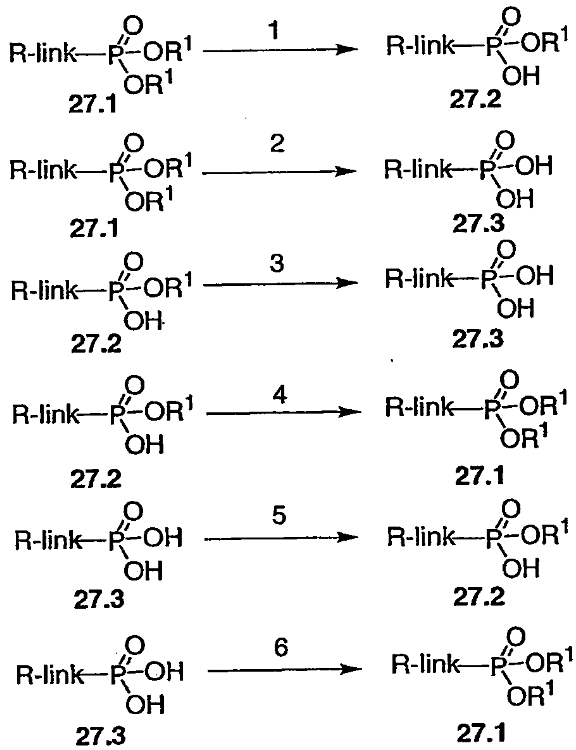
A phosphonic acid R-link-$P(O)(OH)_2$ **27.3** can be transformed into a phosphonate diester R-link-$P(O)(OR^1)_2$ **27.1** (Scheme **27**, Reaction 6) by a coupling reaction with the hydroxy compound R^1OH, in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids **27.3** can be transformed into phosphonic esters **27.1** in which R^1 is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca 70°C. Alternatively, phosphonic acids **27.3** can be transformed into phosphonic esters **27.1** in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester **27.1**.

Scheme 26

Example 2



Scheme 27



General applicability of methods for introduction of phosphonate substituents.

The procedures described above for the conversion of various functional groups into phosphonate moieties are of general application. For example, the methods described above for the introduction of phosphonate groups into the phenylalanine moiety, can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate groups into the thiazole compounds **1.5**, **9.1** and **11.1**, and for the preparation of the phosphonate esters **3**. Similarly, the methods described above for the introduction of phosphonate groups into the thiazole compounds **1.5**, **9.1** and **11.1** can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate groups into the phenylalanine intermediates **4.1** and for the preparation of the compounds **3**.

Phosphonate esters 1-7 incorporating carbamate moieties.

The phosphonate esters **1-7** in which the R^2CO or R^3CO groups are formally derived from the carboxylic acid synthons **14-16**, **19**, **21**, **22**, **25**, **34**, **51** or **52** as shown in Charts **2a**, **2b**, and **2c**, contain a carbamate moiety. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations, A. R. Katritzky, ed., Pergamon, 1995, Vol. 6, p. 416ff, and in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p. 260ff.

Scheme **28** illustrates various methods by which the carbamate linkage can be synthesized. As shown in Scheme **28**, in the general reaction generating carbamates, a carbinol **28.1** is converted into the activated derivative **28.2** in which Lv is a leaving group such as halo, imidazolyl, benztriazolyl and the like, as described below. The activated derivative **28.2** is then reacted with an amine **28.3**, to afford the carbamate product **28.4**. Examples **1 – 7** in Scheme **28** depict methods by which the general reaction can be effected. Examples **8 - 10** illustrate alternative methods for the preparation of carbamates.

Scheme **28**, Example 1 illustrates the preparation of carbamates employing a chloroformyl derivative of the carbinol **28.5**. In this procedure, the carbinol **28.5** is reacted with phosgene, in an inert solvent such as toluene, at about 0°C, as described in Org. Syn. Coll. Vol. 3, 167, 1965, or with an equivalent reagent such as trichloromethoxy chloroformate, as described in Org. Syn. Coll. Vol 6, 715, 1988, to afford the chloroformate **28.6**. The latter compound is

then reacted with the amine component **28.3**, in the presence of an organic or inorganic base, to afford the carbamate **28.7**. cFor example, the chloroformyl compound **28.6** is reacted with the amine **28.3** in a water-miscible solvent such as tetrahydrofuran, in the presence of aqueous sodium hydroxide, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to yield the carbamate **28.7**. cAlternatively, the reaction is preformed in dichloromethane in the presence of an organic base such as diisopropylethylamine or dimethylaminopyridine.

Scheme **28**, Example **2** depicts the reaction of the chloroformate compound **28.6** with imidazole, **28.7**, to produce the imidazolide **28.8**. The imidazolide product is then reacted with the amine **28.3** to yield the carbamate **28.7**. The preparation of the imidazolide is performed in an aprotic solvent such as dichloromethane at 0°C, and the preparation of the carbamate is conducted in a similar solvent at ambient temperature, optionally in the presence of a base such as dimethylaminopyridine, as described in J. Med. Chem., 1989, 32, 357.

Scheme **28** Example **3**, depicts the reaction of the chloroformate **28.6** with an activated hydroxyl compound R"OH, to yield the mixed carbonate ester **28.10**. The reaction is conducted in an inert organic solvent such as ether or dichloromethane, in the presence of a base such as dicyclohexylamine or triethylamine. The hydroxyl component R"OH is selected from the group of compounds **28.19** - **28.24** shown in Scheme **28**, and similar compounds. For example, if the component R"OH is hydroxybenztriazole **28.19**, N-hydroxysuccinimide **28.20**, or pentachlorophenol, **28.21**, the mixed carbonate **28.10** is obtained by the reaction of the chloroformate with the hydroxyl compound in an ethereal solvent in the presence of dicyclohexylamine, as described in Can. J. Chem., 1982, 60, 976. A similar reaction in which the component R"OH is pentafluorophenol **28.22** or 2-hydroxypyridine **28.23** can be performed in an ethereal solvent in the presence of triethylamine, as described in Syn., 1986, 303, and Chem. Ber. 118, 468, 1985.

Scheme **28** Example **4** illustrates the preparation of carbamates in which an alkyloxycarbonylimidazole **28.8** is employed. In this procedure, a carbinol **28.5** is reacted with an equimolar amount of carbonyl diimidazole **28.11** to prepare the intermediate **28.8**. The reaction is conducted in an aprotic organic solvent such as dichloromethane or tetrahydrofuran. The acyloxyimidazole **28.8** is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate **28.7**. The reaction is performed in an aprotic organic solvent such as dichloromethane, as described in Tet. Lett., 42, 2001, 5227, to afford the carbamate **28.7**.

Scheme **28**, Example **5** illustrates the preparation of carbamates by means of an intermediate alkoxycarbonylbenztriazole **28.13**. In this procedure, a carbinol ROH is reacted at ambient temperature with an equimolar amount of benztriazole carbonyl chloride **28.12**, to afford the alkoxycarbonyl product **28.13**. The reaction is performed in an organic solvent such as benzene or toluene, in the presence of a tertiary organic amine such as triethylamine, as described in Syn., 1977, 704. This product is then reacted with the amine $R'NH_2$ to afford the carbamate **28.7**. The reaction is conducted in toluene or ethanol, at from ambient temperature to about 80°C as described in Syn., 1977, 704.

Scheme **28**, Example **6** illustrates the preparation of carbamates in which a carbonate $(R''O)_2CO$, **28.14**, is reacted with a carbinol **28.5** to afford the intermediate alkyloxycarbonyl intermediate **28.15**. The latter reagent is then reacted with the amine $R'NH_2$ to afford the carbamate **28.7**. The procedure in which the reagent **28.15** is derived from hydroxybenztriazole **28.19** is described in Synthesis, 1993, 908; the procedure in which the reagent **28.15** is derived from N-hydroxysuccinimide **28.20** is described in Tet. Lett., 1992, 2781; the procedure in which the reagent **28.15** is derived from 2-hydroxypyridine **28.23** is described in Tet. Lett., 1991, 4251; the procedure in which the reagent **28.15** is derived from 4-nitrophenol **28.24** is described in Syn. 1993, 103. The reaction between equimolar amounts of the carbinol ROH and the carbonate **28.14** is conducted in an inert organic solvent at ambient temperature.

Scheme **28**, Example **7** illustrates the preparation of carbamates from alkoxycarbonyl azides **28.16**. in this procedure, an alkyl chloroformate **28.6** is reacted with an azide, for example sodium azide, to afford the alkoxycarbonyl azide **28.16**. The latter compound is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate **28.7**. The reaction is conducted at ambient temperature in a polar aprotic solvent such as dimethylsulfoxide, for example as described in Syn., 1982, 404.

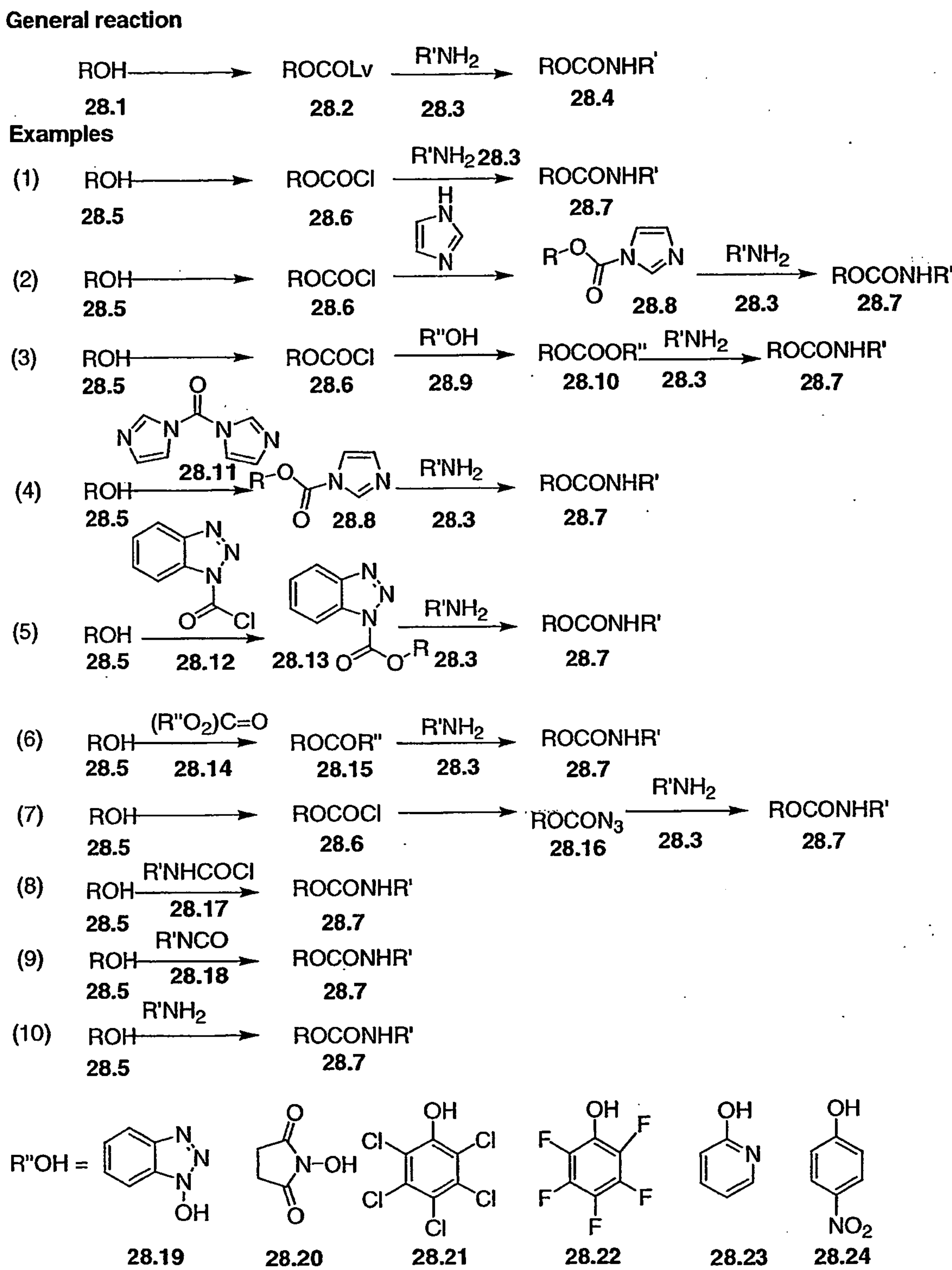
Scheme **28**, Example **8** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and the chloroformyl derivative of an amine. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 647, the reactants are combined at ambient temperature in an aprotic solvent such as acetonitrile, in the presence of a base such as triethylamine, to afford the carbamate **28.7**.

Scheme **28**, Example **9** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an isocyanate **28.18**. In this procedure, which is described in

Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 645, the reactants are combined at ambient temperature in an aprotic solvent such as ether or dichloromethane and the like, to afford the carbamate **28.7**.

Scheme **28**, Example **10** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an amine R'NH$_2$. In this procedure, which is described in Chem. Lett. 1972, 373, the reactants are combined at ambient temperature in an aprotic organic solvent such as tetrahydrofuran, in the presence of a tertiary base such as triethylamine, and selenium. Carbon monoxide is passed through the solution and the reaction proceeds to afford the carbamate **28.7**.

Scheme 28


General reaction
ROH → ROCOLv → ROCONHR'
R'NH2
28.1 28.2 28.3 28.4
Examples
(1) ROH → ROCOCl → ROCONHR'
R'NH2 28.3
28.5 28.6 28.7
(2) ROH → ROCOCl → R'NH2 ROCONHR'
28.5 28.6 28.8 28.3 28.7
(3) ROH → ROCOCl → ROCOOR" → ROCONHR'
R"OH R'NH2
28.5 28.6 28.9 28.10 28.3 28.7
(4) ROH → R'NH2 ROCONHR'
28.11
28.5 28.8 28.3 28.7
(5) ROH → R'NH2 ROCONHR'
28.5 28.12 28.13 28.3 28.7
(6) ROH → ROCOR" → ROCONHR'
(R"O2)C=O R'NH2
28.5 28.14 28.15 28.3 28.7
(7) ROH → ROCOCl → ROCON3 → ROCONHR'
R'NH2
28.5 28.6 28.16 28.3 28.7
(8) ROH → ROCONHR'
R'NHCOCl
28.5 28.17 28.7
(9) ROH → ROCONHR'
R'NCO
28.5 28.18 28.7
(10) ROH → ROCONHR'
R'NH2
28.5 28.7
R"OH =
28.19 28.20 28.21 28.22 28.23 28.24

Preparation of phosphonate intermediates 6 and 7 with phosphonate moieties incorporated into the group R^2COOH and R^3COOH.

The chemical transformations described in Schemes **1-28** illustrate the preparation of compounds **1-5** in which the phosphonate ester moiety is attached to the thiazole substructure, (Schemes **1-3**, **9-10**, and **11-12**), the phenylalanine moiety (Schemes **4-6**), and the benzyl moiety (Schemes **7-8**).

The various chemical methods employed for the preparation of phosphonate groups can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate ester groups into the compounds R^2COOH and R^3COOH, as defined in Charts **2a**, **2b** and **2c**. The resultant phosphonate-containing analogs, designated as $R^{2a}COOH$ and $R^{3a}COOH$ can then, using the procedures described above, be employed in the preparation of the compounds **6** and **7**. The procedures required for the introduction of the phosphonate-containing analogs $R^{2a}COOH$ and $R^{3a}COOH$ are the same as those described above (Schemes **4**, **5**, and **28**) for the introduction of the R^2CO and R^3CO moieties.

<u>Indinavir-like phosphonate protease inhibitors (ILPPI)</u>

Preparation of the intermediate phosphonate esters 1-24.

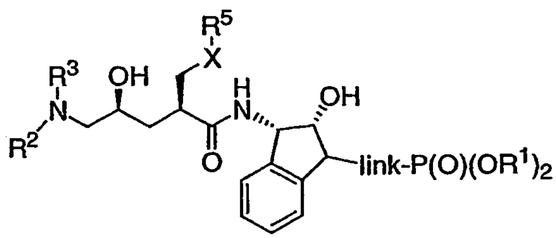
The structures of the intermediate phosphonate esters **1** to **22** and the structures of the component groups R^1, R^4, R^8, $R^{9,}$, R^{11}, X and X' of this invention are shown in Charts **1** - **3**. The structures of the R^2R^3NH components are shown in Chart **4**; the structures of the amines components $R^7NHCH(R^6)CONHR^4$ are shown as the structures **A1** - **A16** in Chart **4**. The structures of the R^5XCH_2 groups are shown in Chart **5**, and those of the $R^{10}CO$ components are illustrated in Chart **6**. The structures of the $R^7NHCH(R^6)COOH$ components are shown in Chart **10**.

Specific stereoisomers of some of the structures are shown in Charts **1** - **10**; however, all stereoisomers are utilized in the syntheses of the compounds **1** to **24**. Subsequent chemical modifications to the compounds **1** to **24**, as described herein, permit the synthesis of the final compounds of this invention.

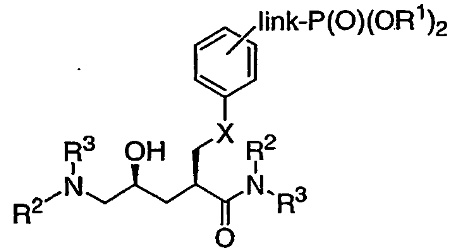
The intermediate compounds **1** to **24** incorporate a phosphonate moiety $(R^1O)_2P(O)$ connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures. Charts **7, 8** and **9** illustrate examples of the linking groups present in the structures **1 – 24.**

Schemes **1 - 207** illustrate the syntheses of the intermediate phosphonate compounds of this invention, **1 - 22**, and of the intermediate compounds necessary for their synthesis. The preparation of the phosphonate esters **23** and **24**, in which a phosphonate moiety is incorporated into one of the groups R^2, R^3, R^5, R^{10} or R^{11} is also described below. In compounds **2, 6, 23** and **24** where two groups are the same Chart 4 it is noted that these groups may be independent or identical.

Chart 1



1



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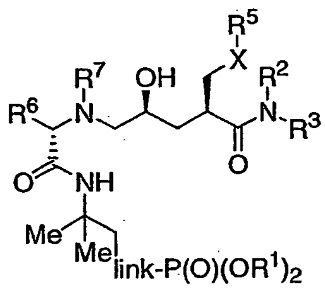

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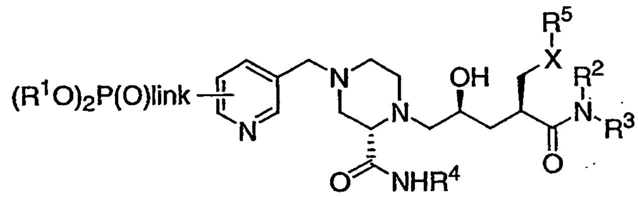

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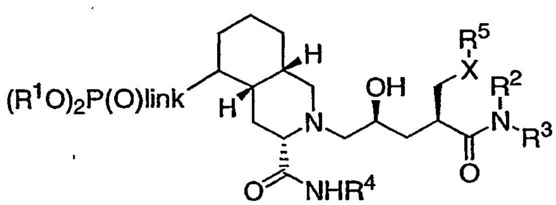

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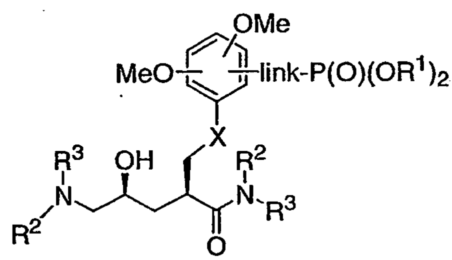

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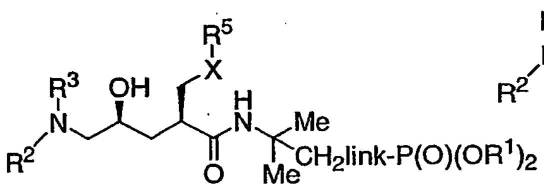

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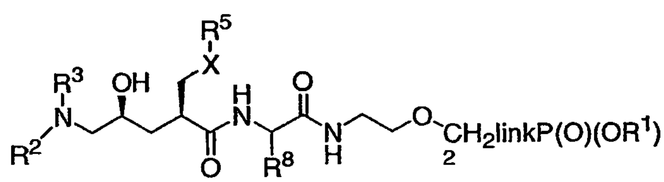
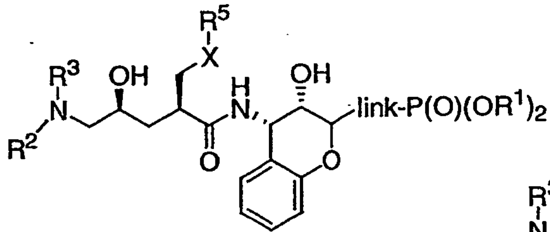


8

R^1 = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl

R^4 = $CH(CH_3)_3$; CH_2CF_3; $CH_2C_6H_4(CH_3)$-2; $CH_2C_6H_3(CH_3)_2$ 2,6

Chart 2



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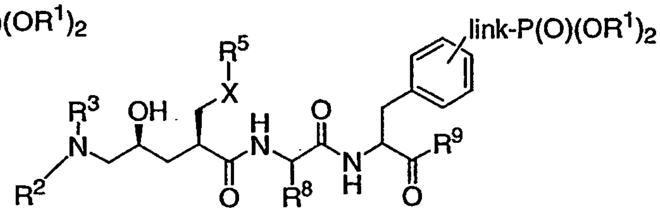

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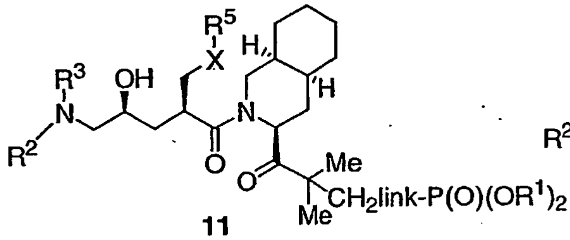

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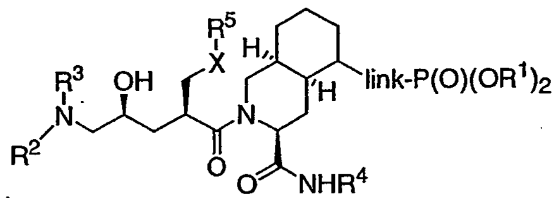

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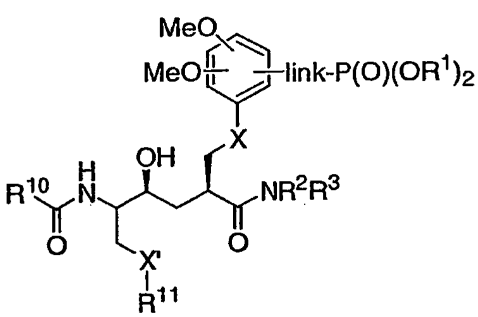
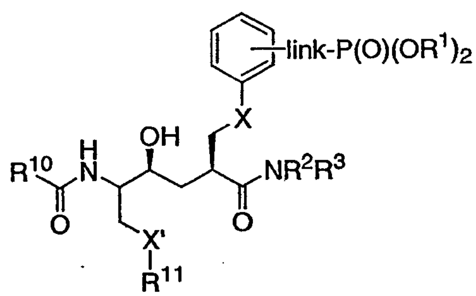


13



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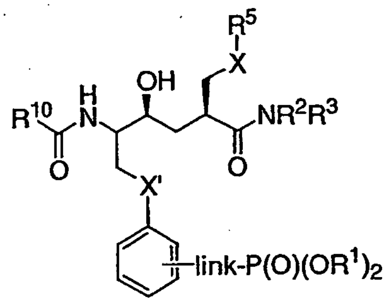

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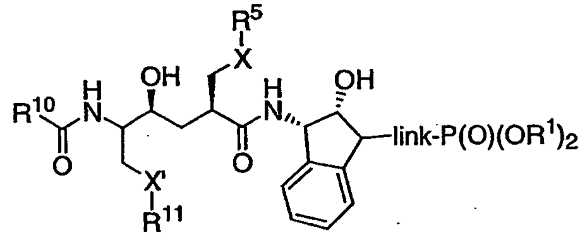

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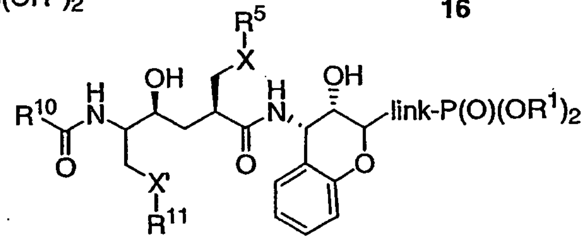


17

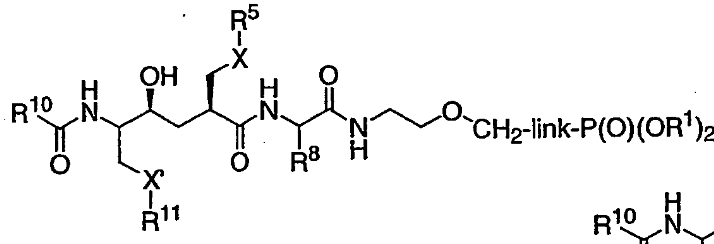
R^{11} = phenyl, alkyl

R^1 = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl

R^4 = $CH(CH_3)_3$; CH_2CF_3; $CH_2C_6H_4(CH_3)$-2; $CH_2C_6H_3(CH_3)_2$ 2,6

R^9 = morpholino or methoxy

Chart 3



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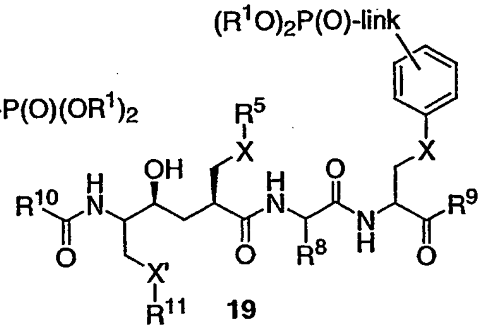

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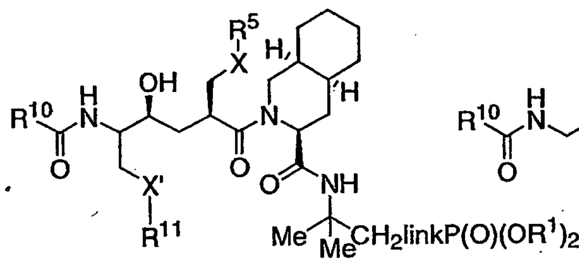

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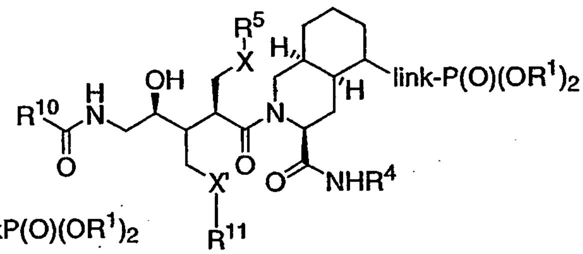

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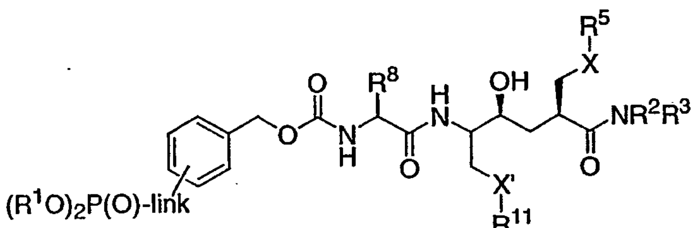

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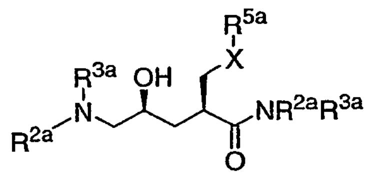

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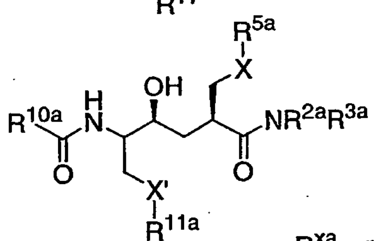


R^{xa} = phosphonate containing R^{x}

24

R^1 = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl

R^4 = $C(CH_3)_3$; CH_2CF_3; $CH_2C_6H_4(CH_3)$-2; $CH_2C_6H_3(CH_3)_2$ 2,6

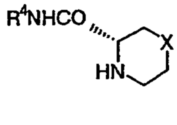
R^8 = alkyl, $CH_2SO_2CH_3$,$C(CH_3)_2SO_2CH_3$,CH_2CONH_2, CH_2SCH_3, imidaz-4-ylmethyl, CH_2NHAc, $CH_2NHCOCF_3$

R^9= morpholino; alkoxy.

R^{11} = phenyl, alkyl

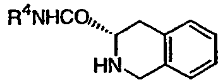
X, X' = S, direct bond

Chart 4 Structures of the R^2R^3NH components



X = NH, CH_2

A1



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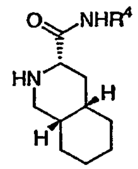
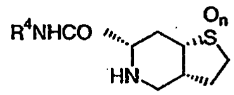
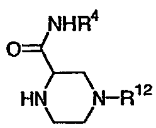


A3



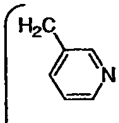
n=0,2

A4

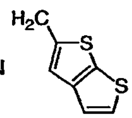


A5

R^{12} =



A6



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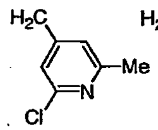

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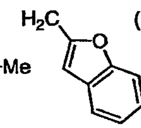

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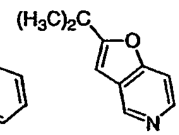
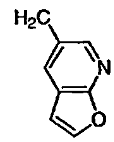


A10



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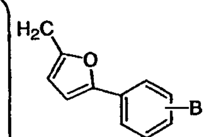
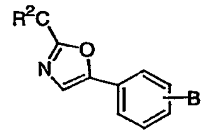


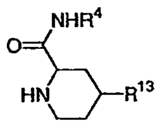
A10a

B= F or Cl



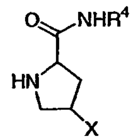
A10b

B= F or Cl
R - Me

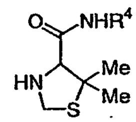


A12

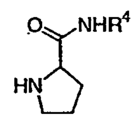
R^{13}=OCH_2Ph
S-3-pyridyl
S-4-pyridyl
OCH_2-4-pyridyl



X = Cl, OMe
A13



A14



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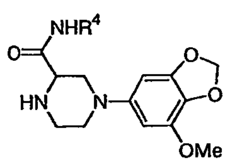

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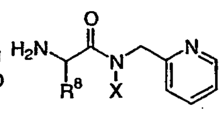
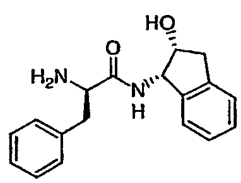


X=H or Me
A17



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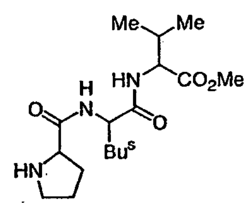

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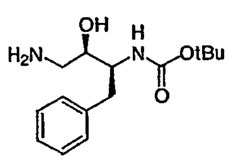

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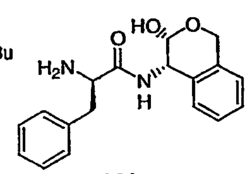
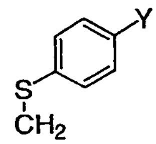


A21

Chart 5. Structures of the R^5XCH_2 groups.

R^5SCH_2 =S-alkyl

24



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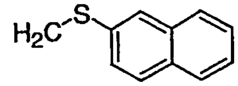
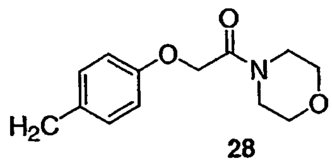
Y = H, F



26

R^5CH_2 = alkyl

27



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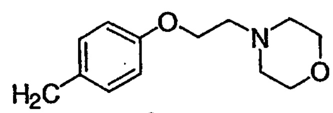

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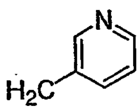

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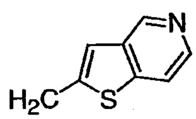

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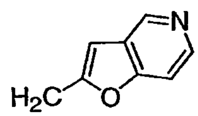

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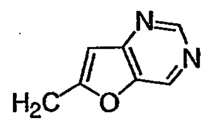

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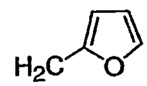

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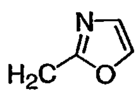

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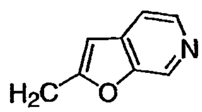

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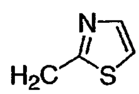

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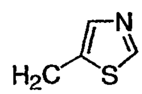

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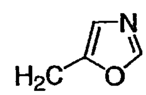

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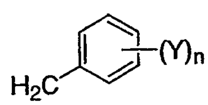


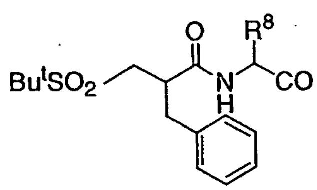
31

Y = H, OC_2H_5, $OCH_2C_6H_5$, MeO, $(MeO)_2$, $(MeO)_3$, CH_2CH_2OH, OH, Ha, CN, Ph, OCH_2O, OCH_2Ph

Chart 6. Structures of the $R^{10}CO$ components

$R^{10}CO$ =alkyl OCO

32



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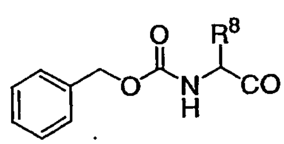
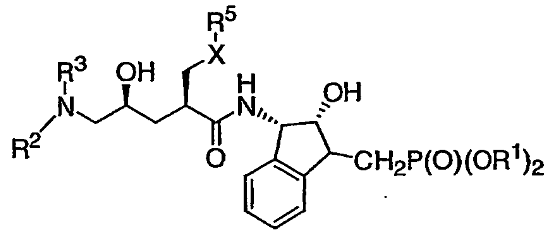
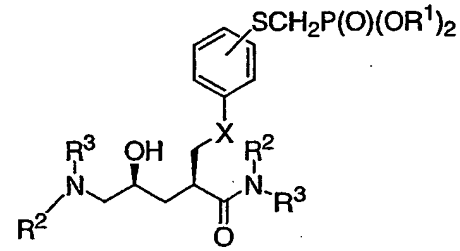


34

Chart 7. Examples of linking groups



L1



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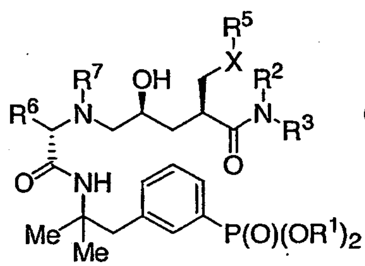

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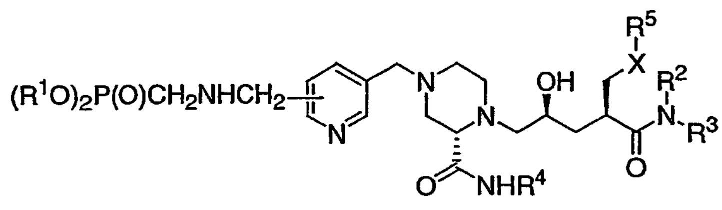

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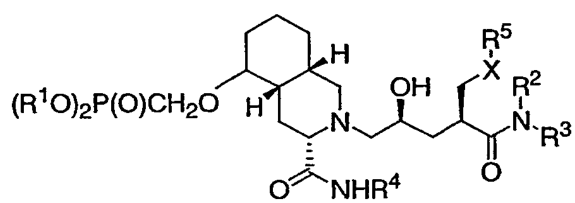

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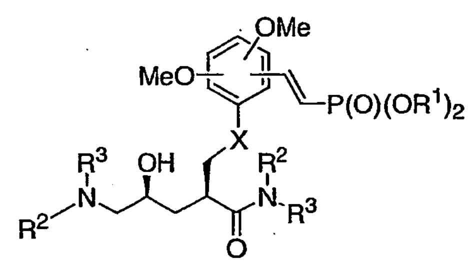

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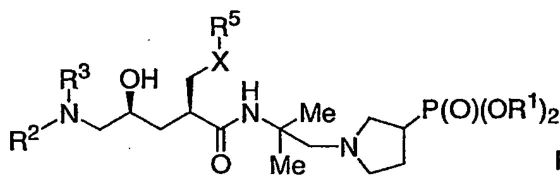

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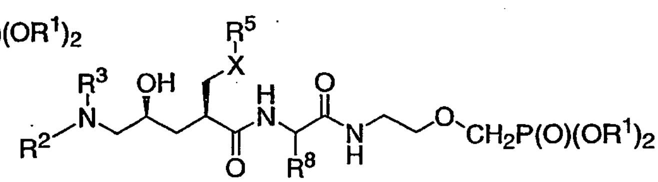
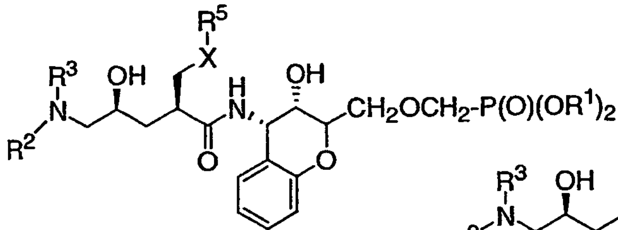


L8

Chart 8. Examples of linking groups



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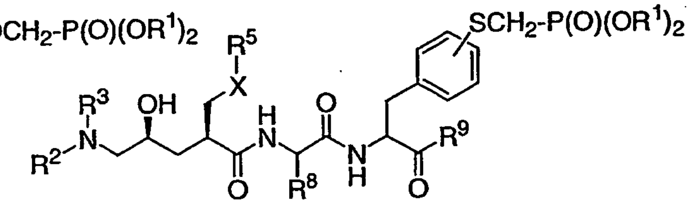

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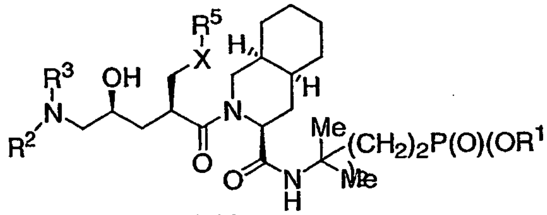

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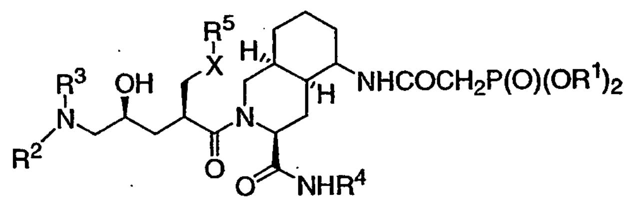

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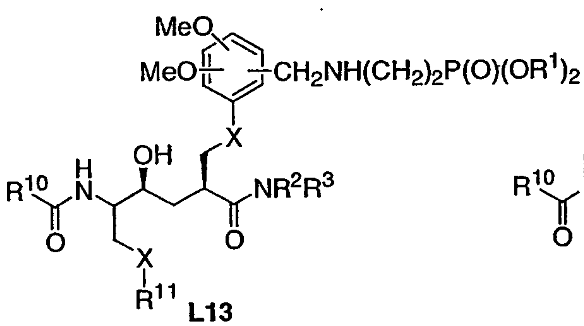

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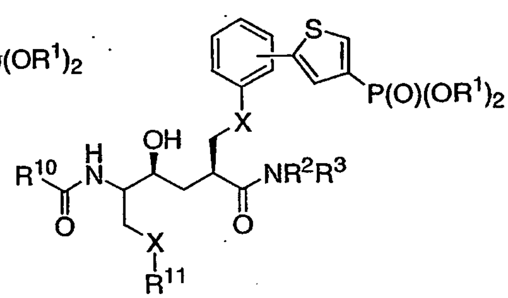

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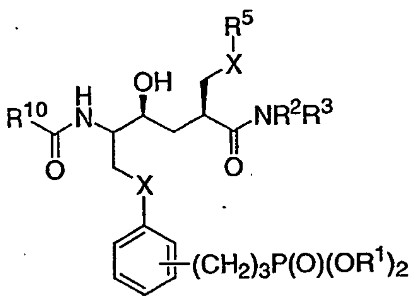

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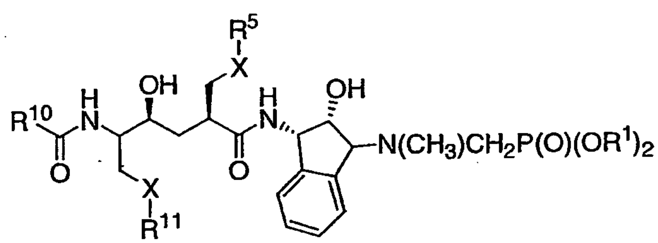

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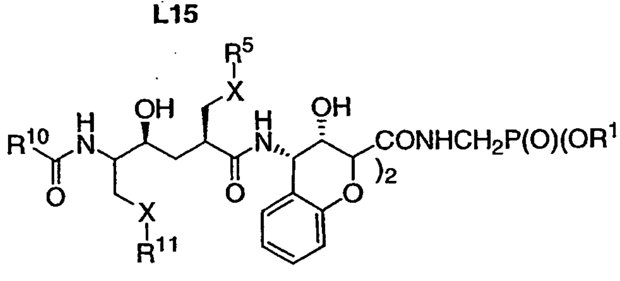
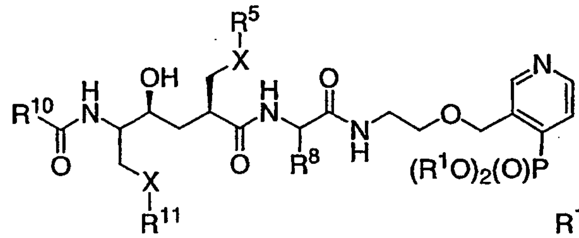
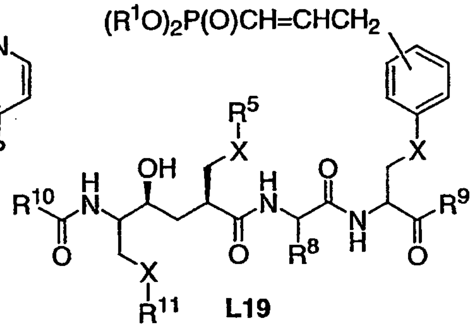


L17

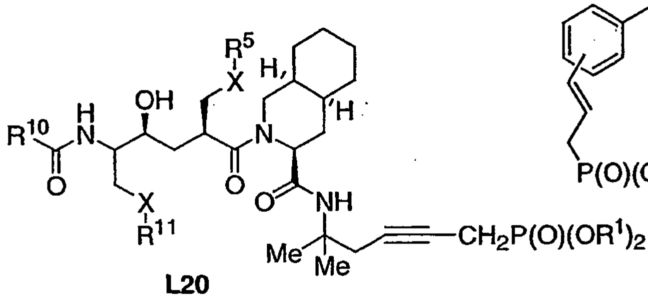
Chart 9. Examples of linking groups



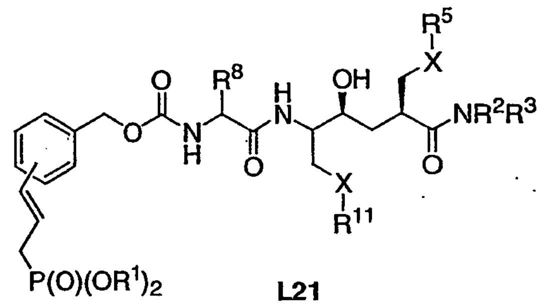
L18



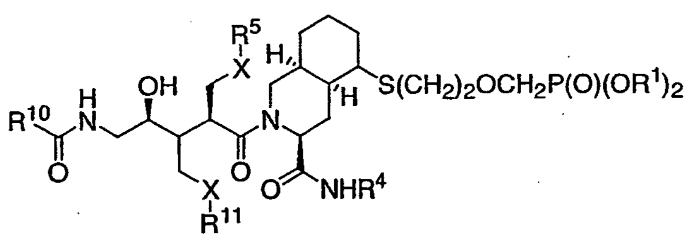
L19



L20

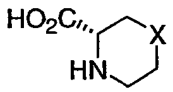


L21



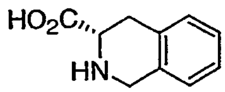
L22

Chart 10. Structures of the $R^7NHCH(R^6)COOH$ components

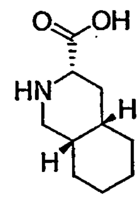


X = NH,CH_2

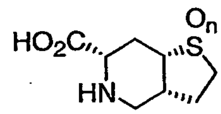
C1



C2

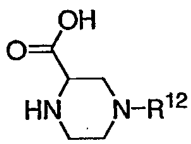


C3



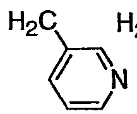
n=0,2

C4

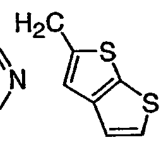


C5

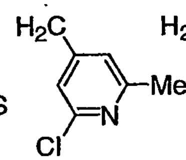
R^{12} =



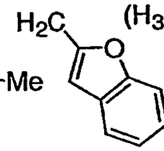
C6



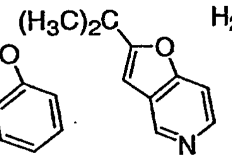
C7



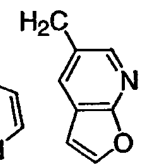
C8



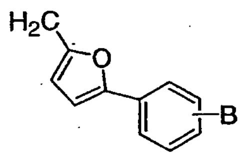
C9



C10

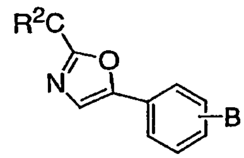


C11



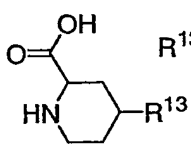
B= F or Cl

C10a



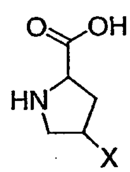
B= F or Cl
R - Me

C10b



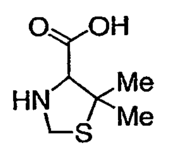
R^{13}= OCH_2Ph
S-3-pyridyl
S-4-pyridyl
OCH_2-4-pyridyl

C12

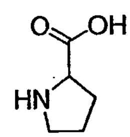


X = Cl, OMe

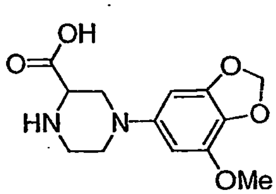
C13



C14



C!5



C16

Protection of reactive substituents.

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH].

Preparation of the phosphonate ester intermediates 1 in which X is a direct bond.

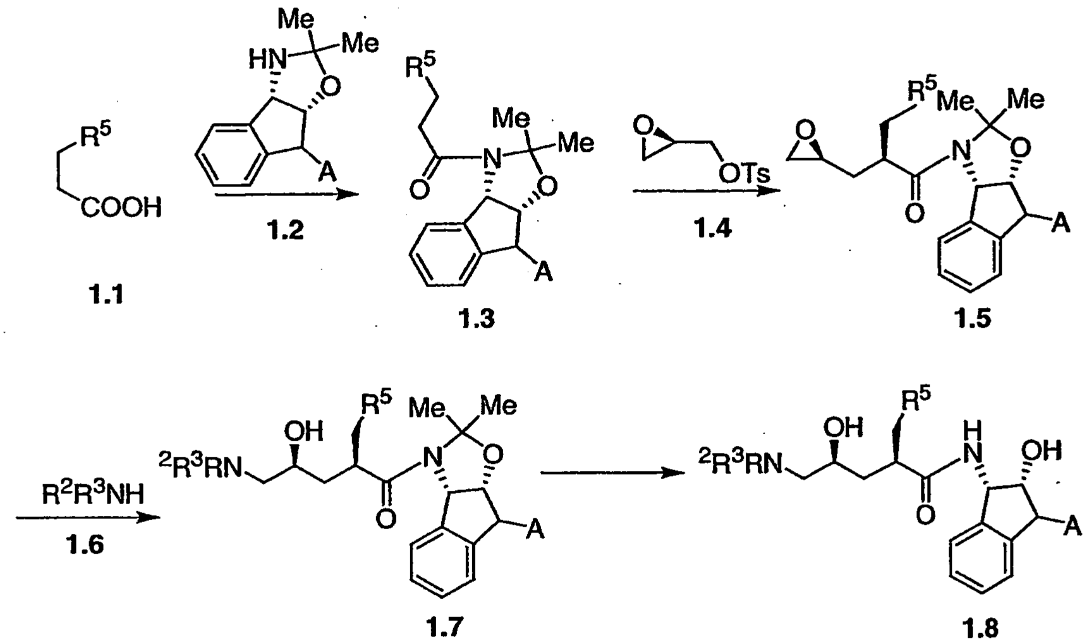
The intermediate phosphonate esters **1**, in which the group A is attached to the aminoindanol moiety, are prepared as shown in Schemes **1** and **2**.
In this procedure, the propionic acid **1.1**, or an activated derivative thereof, is reacted with an aminoindanol derivative **1.2**, in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br, to afford the amide **1.3**. The preparation of the aminoindanol derivatives **1.2** is described in Schemes **133** - **137**.
The preparation of amides from carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.
Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride or anhydride, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.
The conversion of a carboxylic acid into the corresponding acid chloride is effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane.

Preferably, the carboxylic acid **1.1** is reacted with an equimolar amount of the amine **1.2** in the presence of dicyclohexylcarbodiimide and hydroxybenztriazole, in an aprotic solvent such as, for example, tetrahydrofuran, at about ambient temperature, so as to afford the amide product **1.3**. The amide is then reacted with 2-(S)glycidyl tosylate **1.4**, or an equivalent thereof, such as, for example, 2-(S) glycidyl p-nitrobenzenesulfonate, as described in Tet Lett., 35, 673, 1994. To effect the reaction, the amide **1.3** is first converted into the α-anion, by treatment with a strong base, such as, for example, sodium hydride, potassium tert. butoxide and the like. The anion is then reacted with the epoxide **1.4**, or an equivalent, as described above, in an inert solvent such as, for example, dimethylformamide, dioxan and the like. The reaction is conducted at a temperature of from 0°C to -100°C to yield the alkylated product **1.5**. Preferably, equimolar amounts of the amide **1.3** and the epoxide **1.4** are dissolved in tetrahydrofuran at about -50°C, and a slight excess of lithium hexamethyldisilylazide is added, as described in WO 9612492 and Tet. Lett., 35, 673, 1994. The temperature is raised to about -25°C to effect stereoselective alkylation and conversion to the epoxide **1.5**. The thus-obtained epoxide **1.5** is then subjected to a regiospecific ring-opening reaction with the amine **1.6** to yield the hydroxyamine **1.7**. The preparation of hydroxyamines by the reaction between an amine and an epoxide is described, for example, in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1968, p. 357. The amine and the epoxide are reacted together in a polar organic solvent such as, for example, dimethylformamide or an alcohol, to effect the ring-opening reaction. Preferably, equimolar amounts of the amine **1.6** and the epoxide **1.5** are heated in isopropanol at reflux for about 24 hours, to prepare the hydroxyamine product **1.7**, for example as described in WO 9628439 and Tet. Lett., 35, 673, 1994. The hydroxyamine product **1.7** is then deprotected to remove the acetonide group and produce the compound **1.8** in which A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Acetonide protecting groups are removed by treatment with an acid, for example acetic acid or dilute hydrochloric acid, optionally in the presence of water and a water-miscible organic solvent such as, for example, tetrahydrofuran or an alcohol. Preferably, the acetonide protecting group is removed by treatment of the acetonide **1.7** with 6N hydrochloric acid in isopropanol at ambient temperature, as described in WO 9612492, to afford the indanol **1.8**.

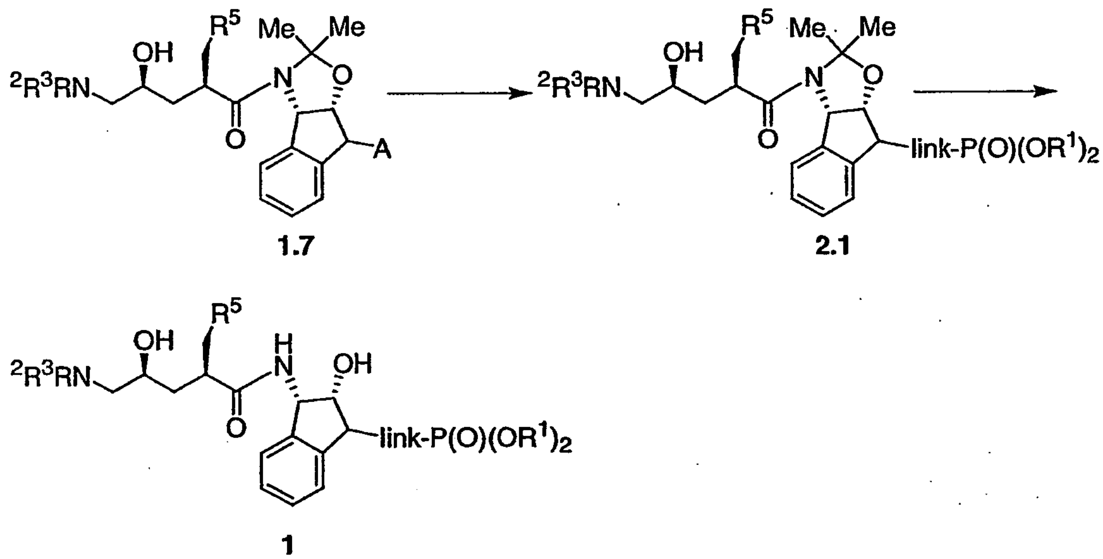
The reactions shown in Scheme **1** illustrate the preparation of the compounds **1.8** in which A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **2** depicts the conversion of the compounds **1.8** in which A is [OH], [SH], [NH], Br, into the compounds **1** in which A is the group link-$P(O)(OR^1)_2$. In this procedure, the compounds **1.7** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **2.1**. Deprotection, by removal of the acetonide protecting group, as described above, then affords the intermediate phosphonate esters **1** in which X is a direct bond.

In the preceding and following schemes, the conversion of various substituents into the group link-$P(O)(OR^1)_2$ can be effected at any convenient stage of the synthetic sequence, or in the final step. The selection of an appropriate step for the introduction of the phosphonate substituent is made after consideration of the chemical procedures required, and the stability of the substrates to those procedures. It may be necessary to protect reactive groups, for example hydroxyl, during the introduction of the group link-$P(O)(OR^1)_2$.
In the preceding and succeeding examples, the nature of the phosphonate ester group can be varied, either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described below (Scheme **199**).

Scheme 1



Scheme 2



Preparation of the phosphonate ester intermediates 1 in which X is sulfur.

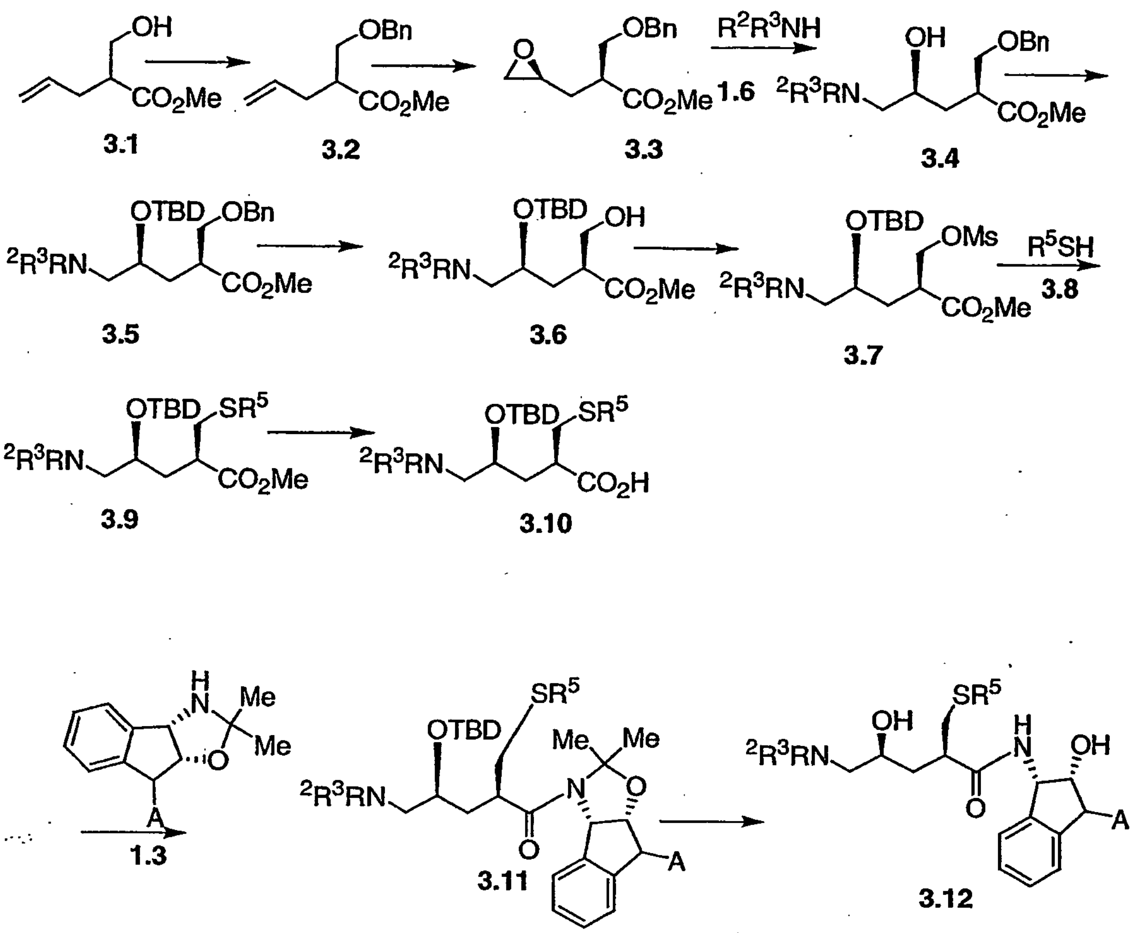
Schemes **3** and **4** illustrate the preparation of the phosphonate esters **1** in which X is sulfur. As shown in Scheme **3**, methyl 2-allyl-3-hydroxypropionate **3.1**, prepared as described in Tet. Lett., 1973, 2429, is converted into the benzyl ether **3.2**. The conversion of alcohols into

benzyl ethers is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 47. The reaction is effected by treatment of the carbinol with a benzyl halide, in the presence of a base such as potassium hydroxide, silver oxide, sodium hydride and the like, in an organic or aqueous organic solvent, optionally in the presence of a phase transfer catalyst. Preferably, the carbinol **3.1** is reacted with benzyl bromide and silver oxide in dimethylformamide at ambient temperature for 48 hours, to afford the product **3.2**. The benzyl ether is then subjected to an epoxidation reaction to produce the epoxide **3.3**. The conversion of olefins into epoxides is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 456. The reaction is performed by the use of a peracid such as peracetic acid, m-chloroperbenzoic acid or monoperphthalic acid, optionally in the presence of a base such as potassium carbonate or sodium bicarbonate, or by the use of tert. butyl hydroperoxide, optionally in the presence of a chiral auxiliary such as diethyl tartrate. Preferably, equimolar amounts of the olefin and m-chloroperbenzoic acid are reacted in dichloromethane in the presence of sodium bicarbonate, as described in Tet. Lett., 849, 1965, to afford the epoxide **3.3**. This compound is then reacted with the amine **1.6** to yield the hydroxyamine **3.4**. The reaction is performed as described above for the preparation of the hydroxyamine **1.7**. The hydroxyl substituent is then protected by conversion to the silyl ether **3.5**, in which OTBD is tert. butyldimethylsilyloxy. The preparation of silyl ethers is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 77. The reaction is effected by treatment of the carbinol with tert. butylchlorodimethylsilane and a base such as imidazole, dimethylaminopyridine or 2,6-lutidine, in an organic solvent such as dichloromethane or dimethylformamide. Preferably, equimolar amounts of the carbinol, tert. butylchlorodimethylsilane and imidazole are reacted in dimethylformamide at ambient temperature to give the silyl ether **3.5**. The benzyl ether is then removed to afford the carbinol **3.6**. The removal of benzyl protecting groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 49. The conversion is effected by means of catalytic hydrogenation over a palladium catalyst, with hydrogen or a hydrogen transfer agent, or by electrolytic reduction, by treatment with trimethylsilyl iodide, or by the use of a Lewis acid such as boron trifluoride or stannic chloride, or by oxidation with ferric chloride or ruthenium dioxide. Preferably, the benzyl ether is removed by reaction of the substrate with 5% palladium on carbon catalyst and ammonium formate in refluxing methanol, as described in Synthesis, 76, 1985. The resultant

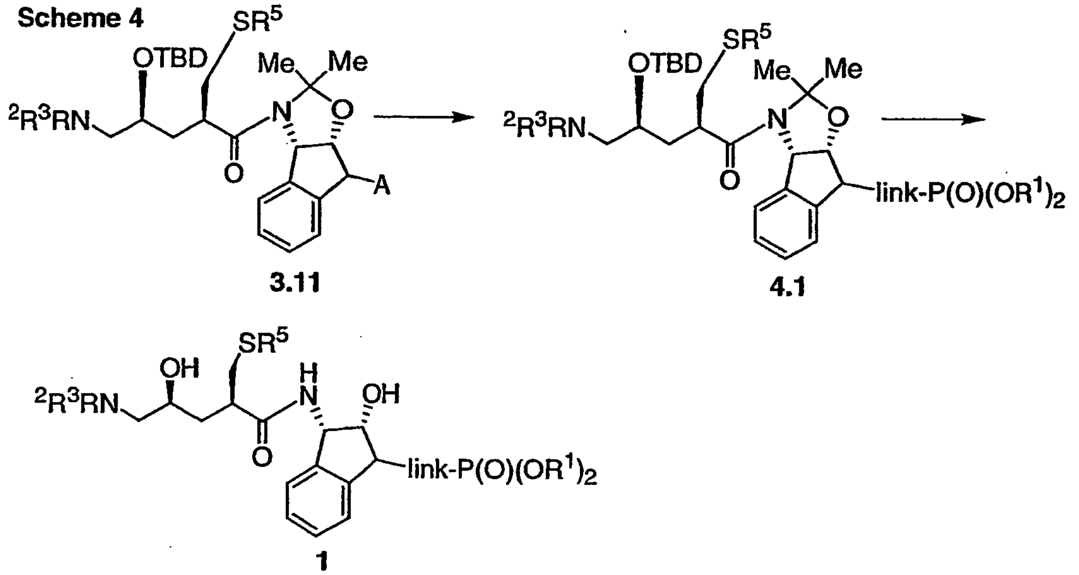
carbinol **3.6** is then converted into the mesylate ester **3.7** by reaction with one molar equivalent of methanesulfonyl chloride or anhydride, in an organic solvent such as dichloromethane, and in the presence of a base such as dimethylaminopyridine or diisopropylethylamine. The product **3.7** is then reacted with the thiol R^5SH, to prepare the thioether **3.9**. The preparation of thioethers by alkylation of thiols is described in Synthetic Organic Chemistry, by R. B. Wagner, H. D. Zook, Wiley, 1953, p. 787. The reaction is effected by treatment of the thiol with a base such as sodium hydroxide, potassium carbonate or diazabicyclononene, in a solvent such as ethanol or dioxan, in the presence of the mesylate **3.7**, to afford the product **3.9**. The methyl ester moiety present in the latter compound is then hydrolyzed to give the carboxylic acid **3.10**. The transformation is effected hydrolytically, for example by the use of an alkali metal hydroxide in an aqueous organic solvent, or enzymically, for example by the use of porcine liver esterase, as described in J. Am. Chem. Soc., 104, 7294, 1982. Preferably, the ester group is hydrolyzed by treatment of the ester **3.9** with one molar equivalent of lithium hydroxide in aqueous methanol at ambient temperature, to give the carboxylic acid **3.10**. The latter compound is then reacted, as described above, with the aminoindanol acetonide **1.3** to give the amide **3.11**. Removal of the acetonide group, as described above, with concomitant desilylation, then affords the hydroxyamide **3.12**.

The reactions shown in Scheme **3** illustrate the preparation of the compounds **3.12** in which A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **4** depicts the conversion of the compounds **3.11** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **1** in which X is sulfur. In this procedure, the compounds **3.11** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **4.1**. Deprotection, by removal of the acetonide protecting group, as described above, then affords the intermediate phosphonate esters **1** in which X is sulfur.

Scheme 3



Scheme 4

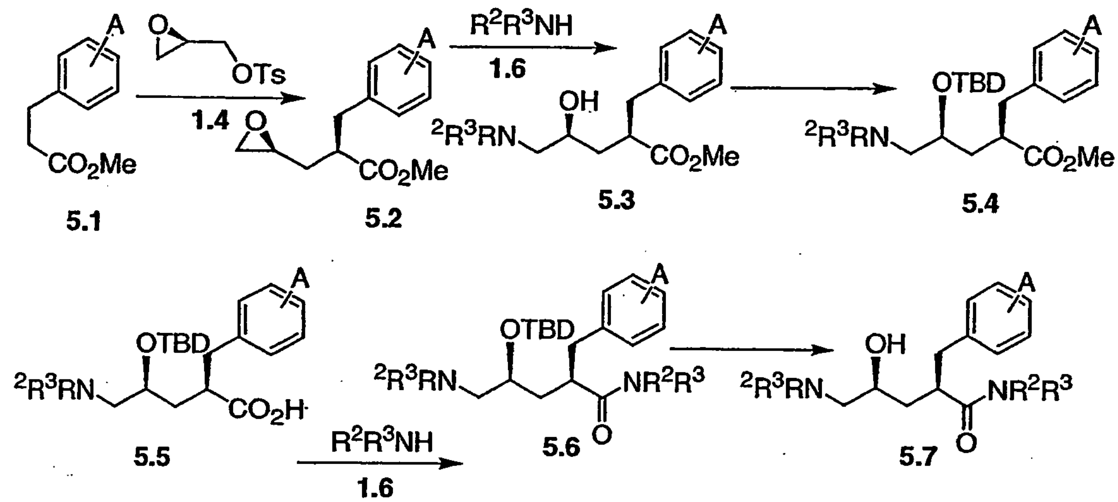


Preparation of the phosphonate ester intermediates 2 in which X is a direct bond.

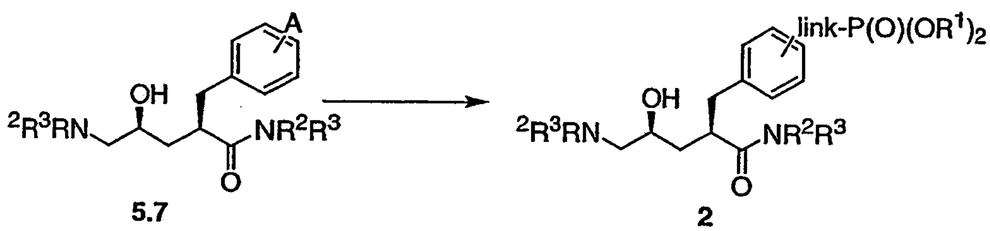
Schemes **5** and **6** illustrate the preparation of the phosphonate esters **2** in which X is a direct bond. As shown in Scheme **5**, the substituted phenyl propionic ester **5.1**, in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br, is reacted with the glycidyl tosylate **1.4** to afford the alkylated product **5.2**. The preparation of the phenylpropionic esters **5.1** is described below, (Schemes **138** - **143**). The reaction is performed as described above for the preparation of the oxirane **1.5**. The product **5.2** is then reacted with the amine R^2R^3NH **(1.6)** to yield the hydroxyamine **5.3**. The reaction is performed as described above for the preparation of the hydroxyamine **1.7**. The secondary hydroxy group is then protected, for example by conversion to the tert. butyldimethyl silyl ether **5.4**, using the conditions described above for the preparation of the silyl ether **3.5**. The methyl ester is then hydrolyzed to produce the carboxylic acid **5.5**, using the conditions described above for the hydrolysis of the methyl ester **3.9**. The carboxylic acid is then coupled with the amine **1.6** to give the amide **5.6**. The reaction is effected under the conditions described above for the preparation of the amide **1.3**. The product is desilylated, for example by treatment with 1M tetrabutyl ammonium fluoride in tetrahydrofuran, as described in J. Am. Chem. Soc., 94, 6190, 1972, to give the carbinol **5.7**.

The reactions shown in Scheme **5** illustrate the preparation of the compounds **5.7** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br, as described herein. Scheme **6** depicts the conversion of the compounds **5.7** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **2** in which X is a direct bond. In this procedure, the compounds **5.7** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **2**.

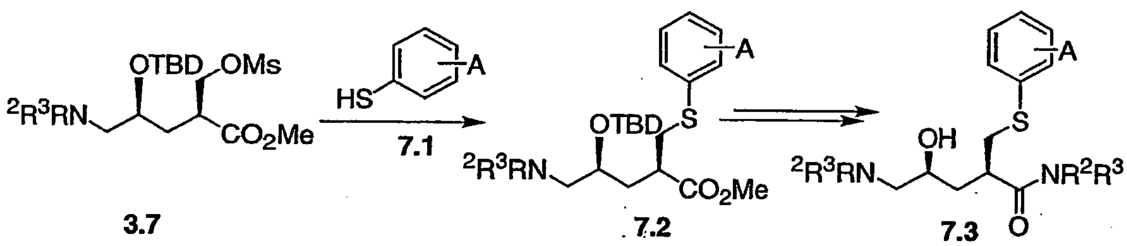
Scheme 5



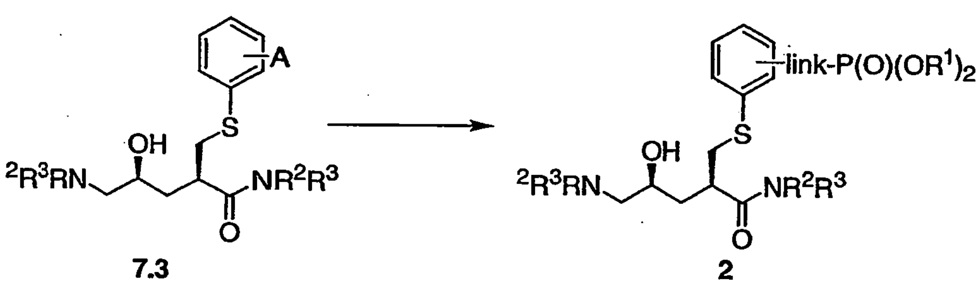
Scheme 6



Scheme 7



Scheme 8



Preparation of the phosphonate ester intermediates 2 in which X is sulfur.

Schemes **7** and **8** illustrate the preparation of the phosphonate esters **2** in which X is sulfur. As shown in Scheme **7**, the mesylate **3.7** is reacted with the thiophenol **7.1**, in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br, to afford the thioether **7.2**. The reaction is performed under the same conditions as described above for the preparation of the thioether **3.9**. The preparation of the thiophenols **7.2** is described in Schemes **144 - 153**. The product **7.2** is then transformed, using the sequence of reactions described above for the conversion of the ester **5.4** into the aminoamide **5.7**, into the aminoamide **7.3**.

The reactions shown in Scheme **7** illustrate the preparation of the compounds **7.3** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **8** depicts the conversion of the compounds **7.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **2** in which X is sulfur. In this procedure, the compounds **7.3** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **2**.

Preparation of the phosphonate ester intermediates 3 in which X is a direct bond.

Schemes **9** and **10** illustrate the preparation of the phosphonate esters **3** in which X is a direct bond. As shown in Scheme **9**, the methyl ester **9.1** is reacted, as described above, (Scheme **1**) with the epoxide **1.4** to afford the alkylated ester **9.2**. The product is then reacted with the amine **9.3**, in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor, to yield the hydroxyamine **9.4**. The preparation of the tert. butylamine derivatives **9.3** is described below, (Schemes **154 - 158**). The hydroxyamine is then transformed, using the sequence of reactions described above for the conversion of the aminoester **5.3** into the aminoamide **5.7**, into the aminoamide **9.5**.

The reactions shown in Scheme **9** illustrate the preparation of the compounds **9.5** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **10** depicts the conversion of the compounds **9.5** in which A is [OH], [SH], [NH],

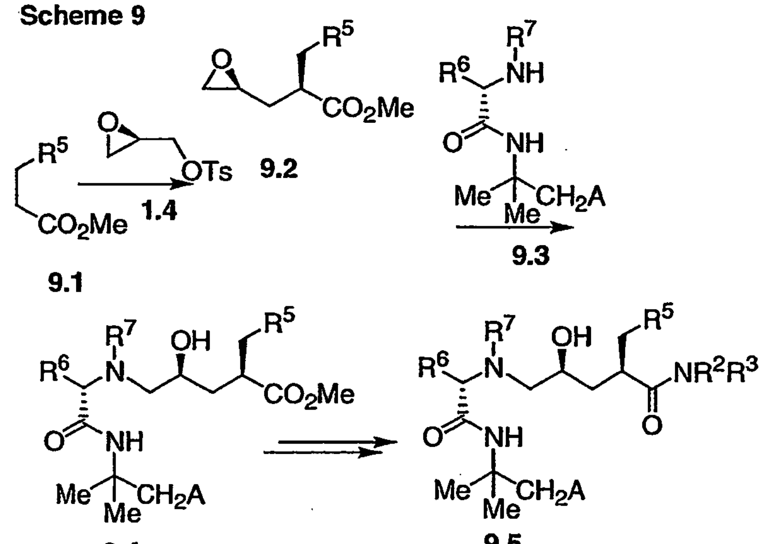
Br, into the phosphonate esters **3** in which X is a direct bond. In this procedure, the compounds **9.5** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **3**.

Preparation of the phosphonate ester intermediates 3 in which X is sulfur.

Schemes **11** and **12** illustrate the preparation of the phosphonate esters **3** in which X is sulfur. As shown in Scheme **11**, the benzyl-protected oxirane **3.3** is reacted, as described above, with the substituted tert. butylamine **9.3** to afford the hydroxyamine **11.1**. The product is then converted, using the sequence of reactions shown in Scheme **5** for the conversion of the hydroxyamine **5.3** into the aminoamide **5.7**, into the aminoamide **11.2**.

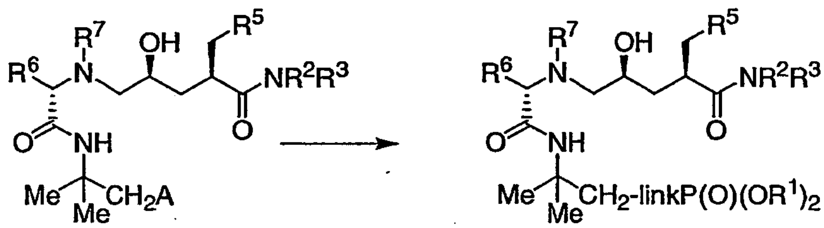
The reactions shown in Scheme **11** illustrate the preparation of the compounds **11.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **12** depicts the conversion of the compounds **11.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **3** in which X is sulfur. In this procedure, the compounds **11.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **3**.

Scheme 9



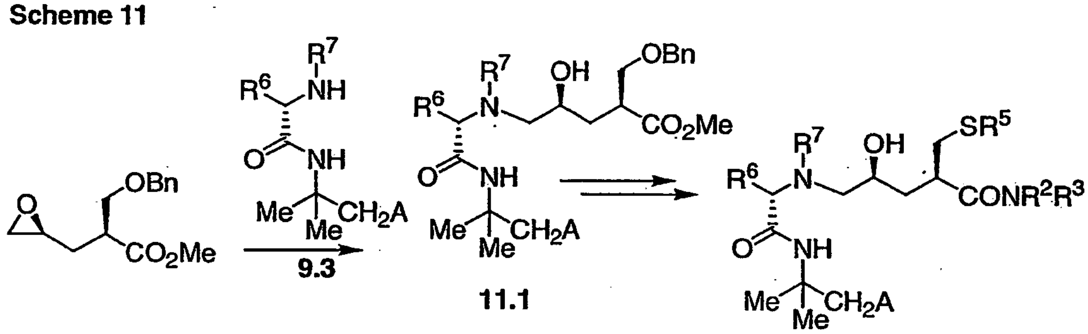
9.1 9.2 1.4 9.3 9.4 9.5

Scheme 10



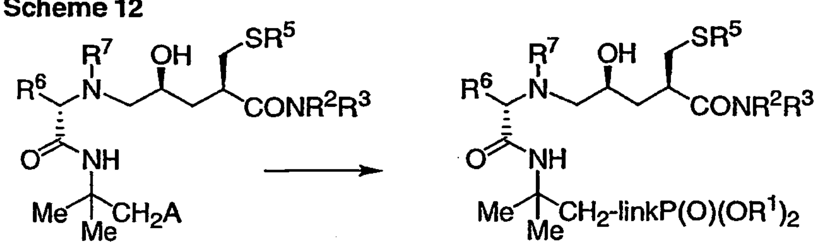
9.5 3

Scheme 11



3.3 9.3 11.1 11.2

Scheme 12



11.2 3

Preparation of the phosphonate ester intermediates 4 in which X is a direct bond.

Schemes **13** and **14** illustrate the preparation of the phosphonate esters **4** in which X is a direct bond. As shown in Scheme **13**, the oxirane **9.2** is reacted, as described in Scheme **1**, with the pyridyl piperazine derivative **13.1** to produce the hydroxyamine **13.2**. The preparation of the pyridyl piperazine derivatives **13.1** is described in Schemes **159 – 164**. The product is then transformed, as described previously, (Scheme **5**) into the amide **13.3**.

The reactions shown in Scheme **13** illustrate the preparation of the compounds **13.3** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **12** depicts the conversion of the compounds **13.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **4** in which X is a direct bond. In this procedure, the compounds **13.3** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **4**.

Preparation of the phosphonate ester intermediates 4 in which X is sulfur.

Schemes **15** and **16** illustrate the preparation of the phosphonate esters **4** in which X is sulfur. As shown in Scheme **15**, the benzyl-protected oxirane **3.3** is reacted, as described above, with the pyridyl piperazine derivative **13.1** to afford the hydroxyamine **15.1**. The product is then converted, as described above (Scheme **5**) into the aminoamide **15.2**.

The reactions shown in Scheme **15** illustrate the preparation of the compounds **15.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **16** depicts the conversion of the compounds **15.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **4** in which X is sulfur. In this procedure, the compounds **15.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **4**.

Preparation of the phosphonate ester intermediates 5 in which X is a direct bond.

Schemes **17** and **18** illustrate the preparation of the phosphonate esters **5** in which X is a direct bond. As shown in Scheme **17**, the oxirane **9.2** is reacted, as described in Scheme **1**, with the decahydroisoquinoline derivative **17.1** to produce the hydroxyamine **17.2**. The preparation of the decahydroisoquinoline derivatives **17.1** is described in Schemes **192 – 197**. The product is then transformed, as described previously, (Scheme **3**) into the amide **17.3**.

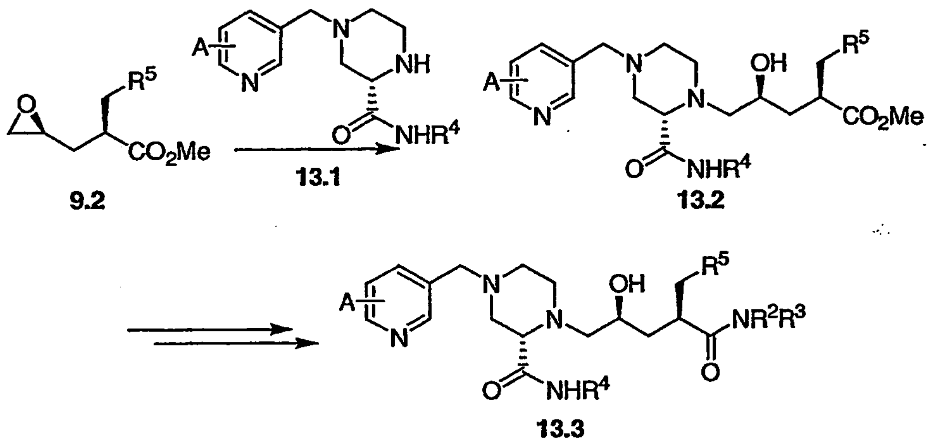
The reactions shown in Scheme **17** illustrate the preparation of the compounds **17.3** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **18** depicts the conversion of the compounds **17.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **5** in which X is a direct bond. In this procedure, the compounds **17.3** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **5**.

Preparation of the phosphonate ester intermediates 5 in which X is sulfur.

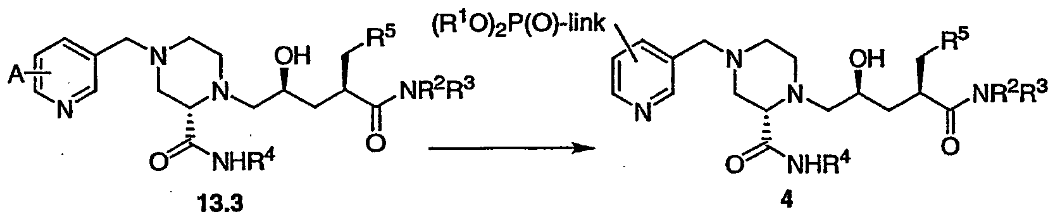
Schemes **19** and **20** illustrate the preparation of the phosphonate esters **5** in which X is sulfur. As shown in Scheme **19**, the benzyl-protected oxirane **3.3** is reacted, as described above, with the decahydroisoquinoline derivative **17.1** to afford the hydroxyamine **19.1**. The product is then converted, as described above (Scheme **5**) into the aminoamide **19.2**.

The reactions shown in Scheme **19** illustrate the preparation of the compounds **19.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **20** depicts the conversion of the compounds **19.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **5** in which X is sulfur. In this procedure, the compounds **19.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **5**.

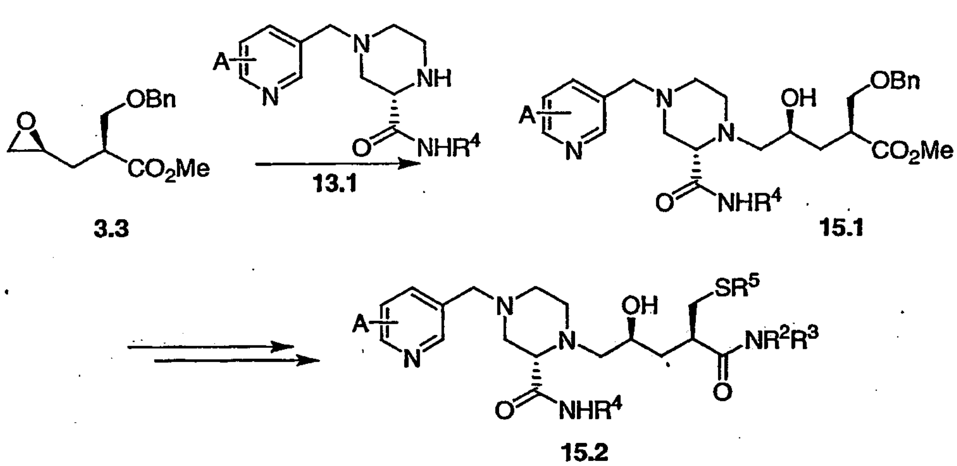
Scheme 13



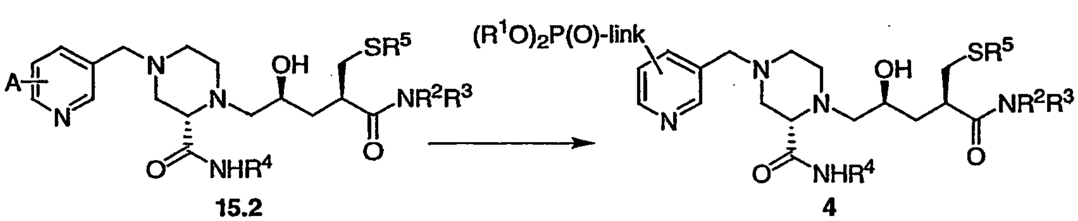
Scheme 14



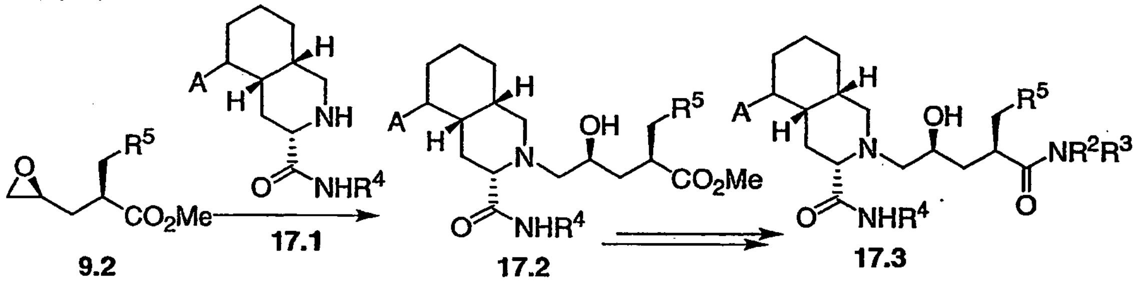
Scheme 15



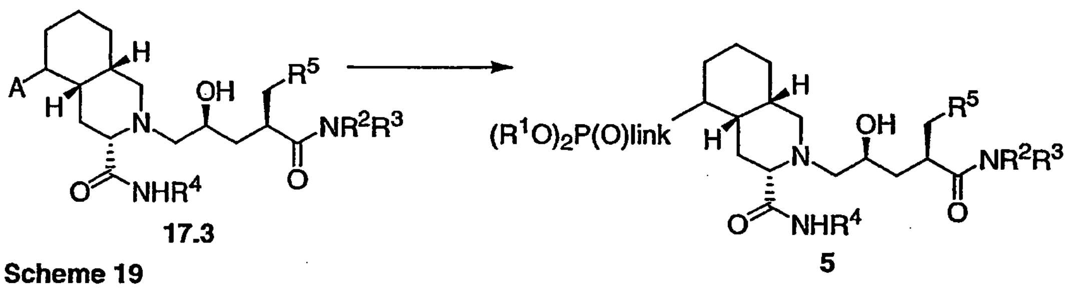
Scheme 16



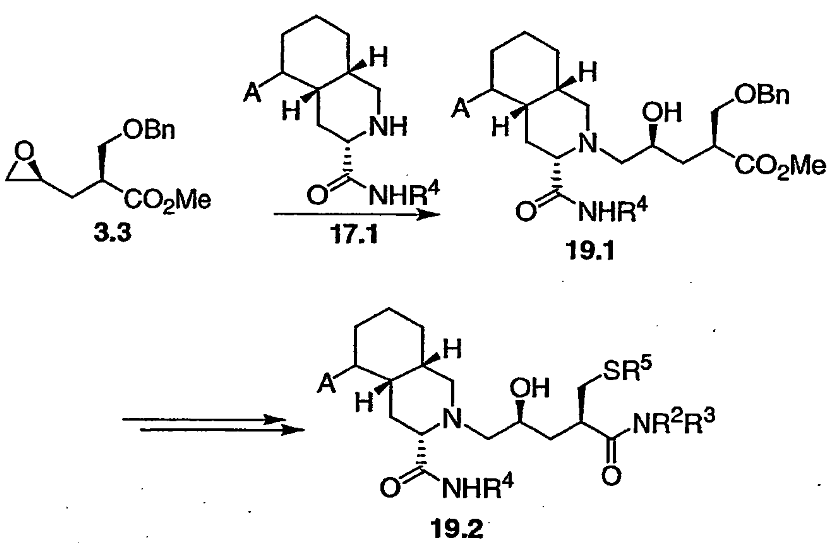
Scheme 17



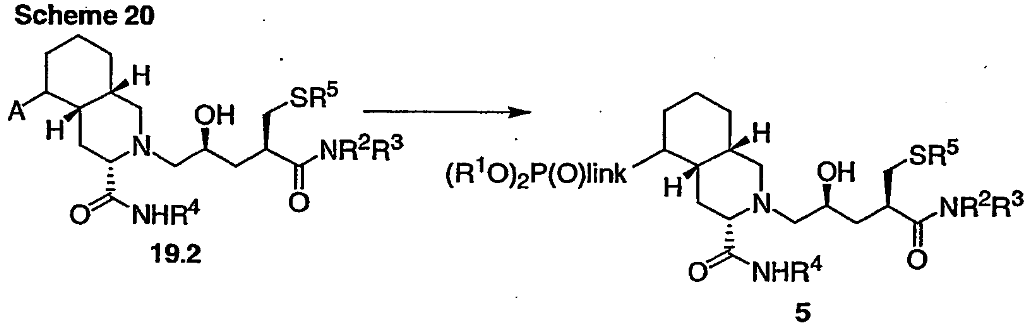
Scheme 18



Scheme 19



Scheme 20



Preparation of the phosphonate ester intermediates 6 in which X is a direct bond.

Schemes **21** and **22** illustrate the preparation of the phosphonate esters **6** in which X is a direct bond. As shown in Scheme **21**, the glycidyl tosylate **1.4** is reacted, as described in Scheme **5**, with the anion of the dimethoxyphenyl propionic ester **21.1** to afford the alkylated product **21.2**. The preparation of the dimethoxyphenyl propionic ester derivatives **21.1** is described in Scheme **186**. The product is then transformed, as described previously, (Scheme **5**) into the amide **21.3**.

The reactions shown in Scheme **21** illustrate the preparation of the compounds **21.3** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **22** depicts the conversion of the compounds **21.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **6** in which X is a direct bond. In this procedure, the compounds **21.3** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **6**.

Preparation of the phosphonate ester intermediates 6 in which X is sulfur.

Schemes **23** and **24** illustrate the preparation of the phosphonate esters **6** in which X is sulfur. As shown in Scheme **23**, the mesylate **3.7** is reacted, as described in Scheme **3**, with the dimethoxyphenyl mercaptan **23.1** to yield the thioether **23.2**. The preparation of the substituted thiols **23.1** is described below in Schemes **170** – **173**. The product is then converted, as described above (Scheme **5**) into the aminoamide **23.3**.

The reactions shown in Scheme **23** illustrate the preparation of the compounds **23.3** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **24** depicts the conversion of the compounds **23.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **6** in which X is sulfur. In this procedure, the compounds **23.3** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **6**.

Preparation of the phosphonate ester intermediates 7 in which X is a direct bond.

Schemes **25** and **26** illustrate the preparation of the phosphonate esters **7** in which X is a direct bond. As shown in Scheme **25**, the oxirane **9.2** is reacted, as described above (Scheme **1**) with the amine **1.6** to afford the hydroxyamine **25.1**. The product is then converted into the silyl ether **25.2**, using the procedures described in Scheme **3**. The methyl ester is then hydrolyzed to give the carboxylic acid **25.3**, and this compound is then coupled with the tert. butylamine derivative **25.4**, using the procedures described in Scheme **1**, to yield the amide **25.5**. The preparation of the tert. butylamine derivatives **25.4** is described in Schemes **154 – 157**. Desilylation then produces the hydroxyamide **25.6**.

The reactions shown in Scheme **25** illustrate the preparation of the compounds **25.6** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **26** depicts the conversion of the compounds **25.6** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **7** in which X is a direct bond. In this procedure, the compounds **25.6** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **7**.

Preparation of the phosphonate ester intermediates 7 in which X is sulfur.

Schemes **27** and **28** illustrate the preparation of the phosphonate esters **7** in which X is sulfur. As shown in Scheme **27**, the carboxylic acid **3.10** is coupled, as described in Scheme **3**, with the tert. butylamine derivative **25.4** to yield the amide product **27.1**. The product is then desilylated, as described above, to afford the amide **27.2**.

The reactions shown in Scheme **27** illustrate the preparation of the compounds **27.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **28** depicts the conversion of the compounds **27.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **7** in which X is sulfur. In this procedure, the compounds **27.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **7**.

Preparation of the phosphonate ester intermediates 8 in which X is a direct bond.

Schemes **29** and **30** illustrate the preparation of the phosphonate esters **8** in which X is a direct bond. As shown in Scheme **29**, the silylated carboxylic acid **25.3** is coupled, as described above, (Scheme **1**) with the amine **29.1** to afford the amide **29.2** which upon desilylation produces the hydroxyamide **29.3**. The preparation of the ethanolamine derivatives **29.1** is described in Schemes **174 – 178**.

The reactions shown in Scheme **29** illustrate the preparation of the compounds **29.3** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **30** depicts the conversion of the compounds **29.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **8** in which X is a direct bond. In this procedure, the compounds **29.3** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **8**.

Preparation of the phosphonate ester intermediates 8 in which X is sulfur.

Schemes **31** and **32** illustrate the preparation of the phosphonate esters **8** in which X is sulfur. As shown in Scheme **31**, the carboxylic acid **3.10** is coupled, as described previously, with the ethanolamine derivative **29.1** to yield the amide; the product is then desilylated, as described above, to afford the hydroxyamide **31.1**.

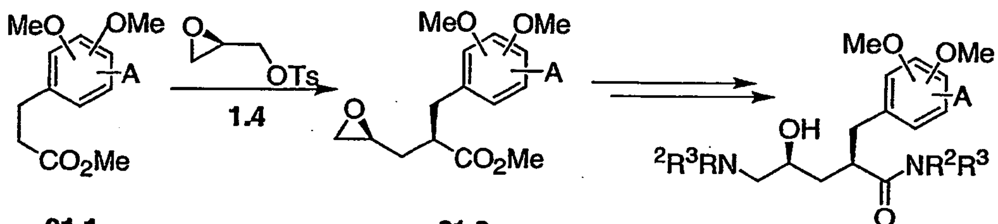
The reactions shown in Scheme **31** illustrate the preparation of the compounds **31.1** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **32** depicts the conversion of the compounds **31.1** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **8** in which X is sulfur. In this procedure, the compounds **31.1** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **8**.

Preparation of the phosphonate ester intermediates 9 in which X is a direct bond.

Schemes **33** and **34** illustrate the preparation of the phosphonate esters **9** in which X is a direct bond. As shown in Scheme **33**, the silylated carboxylic acid **25.3** is coupled, as described above, (Scheme **1**) with the chroman amine **33.1** to afford the corresponding amide, which upon desilylation produces the hydroxyamide **33.2**. The preparation of the chroman amines **33.1** is described in Schemes **179 – 181a**.

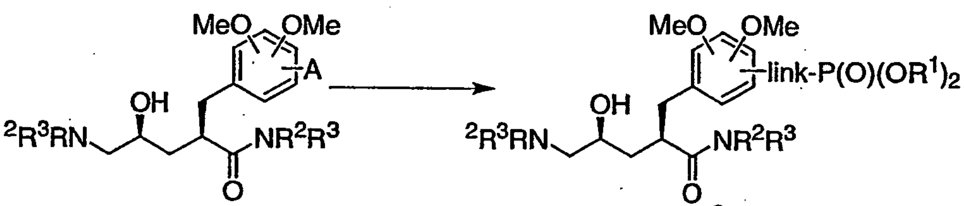
The reactions shown in Scheme **33** illustrate the preparation of the compounds **33.2** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **34** depicts the conversion of the compounds **33.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **9** in which X is a direct bond. In this procedure, the compounds **33.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **9**.

Scheme 21



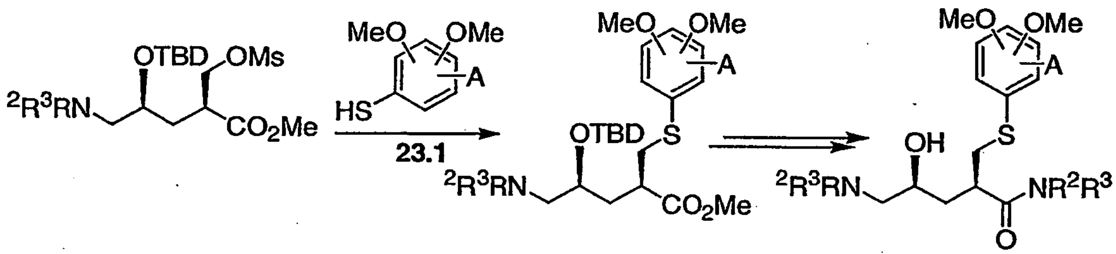
21.1 21.2 21.3

Scheme 22



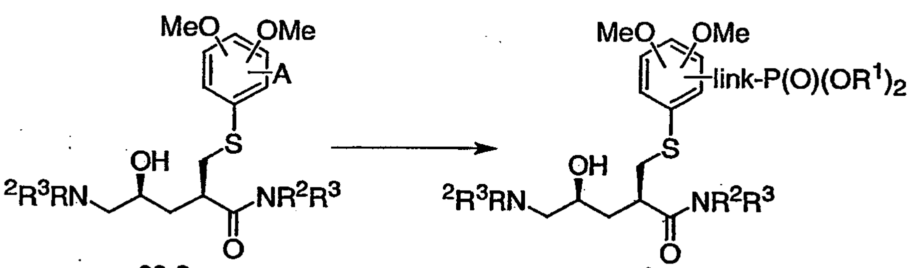
21.3 6

Scheme 23



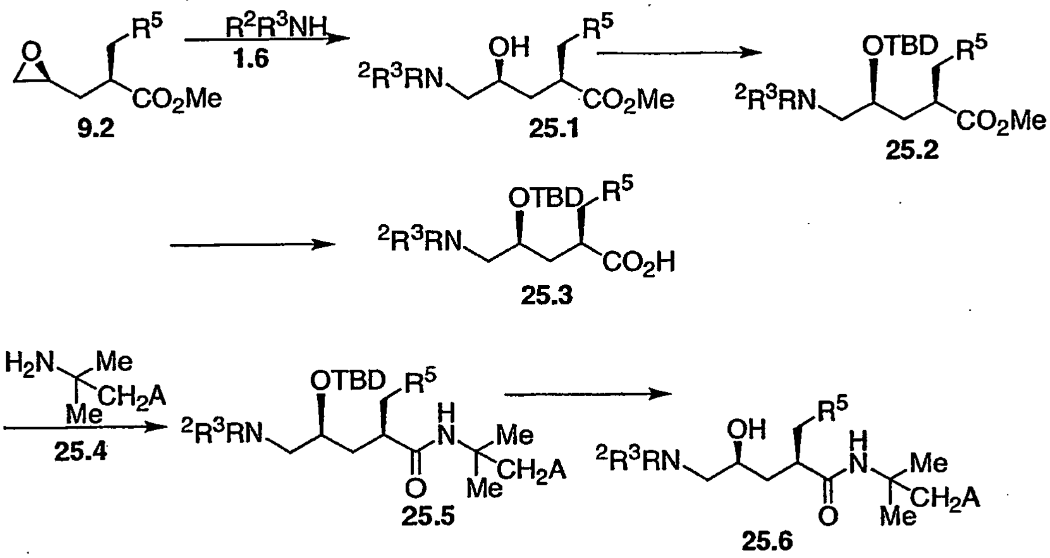
3.7 23.2 23.3

Scheme 24

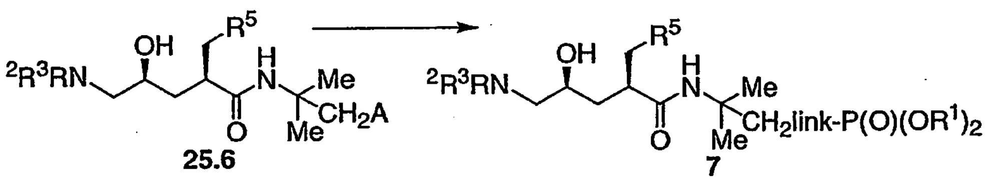


23.3 6

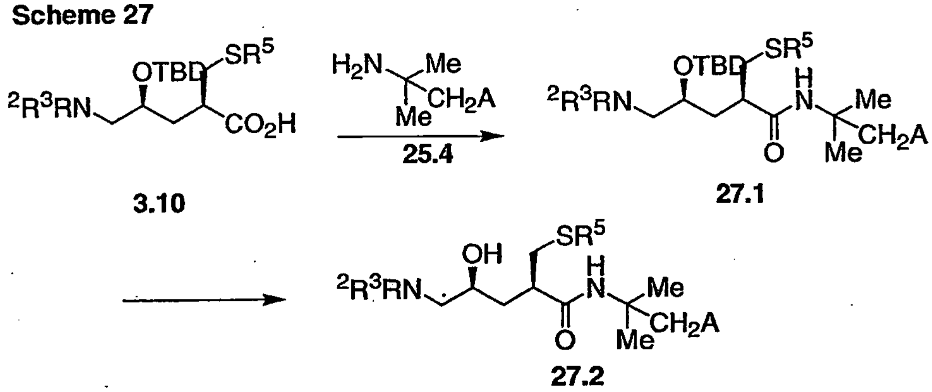
Scheme 25



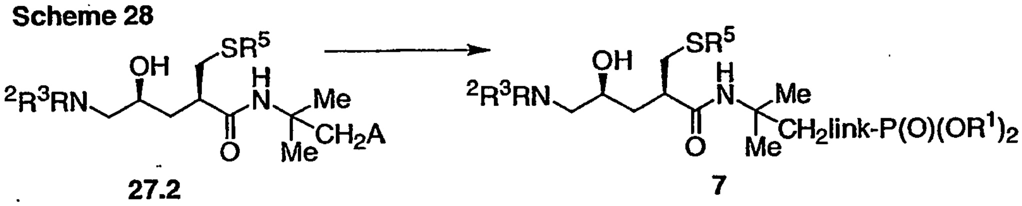
Scheme 26



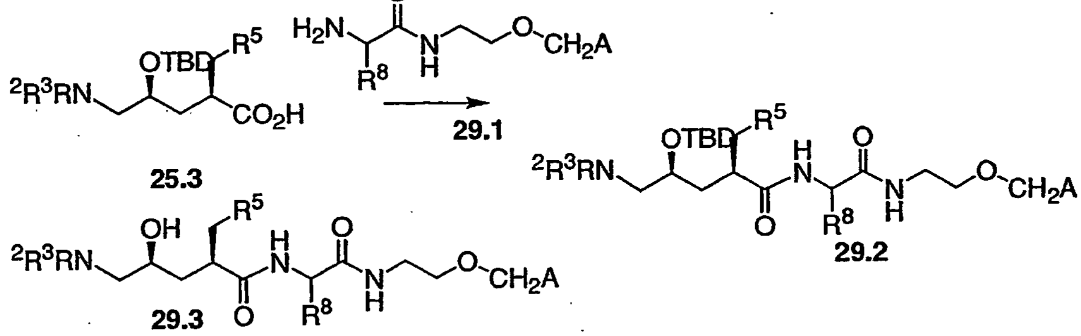
Scheme 27



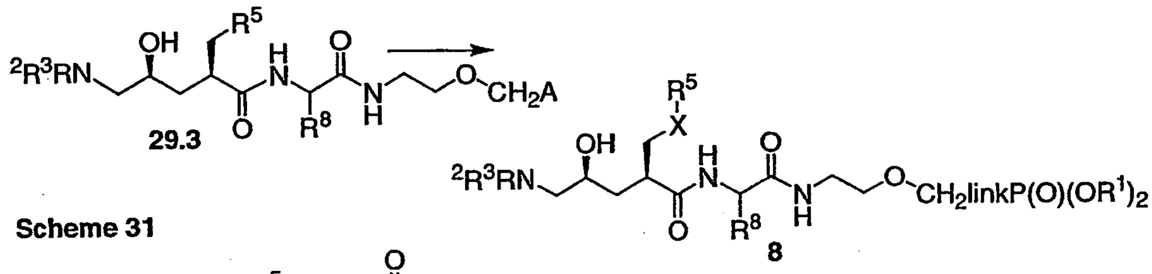
Scheme 28



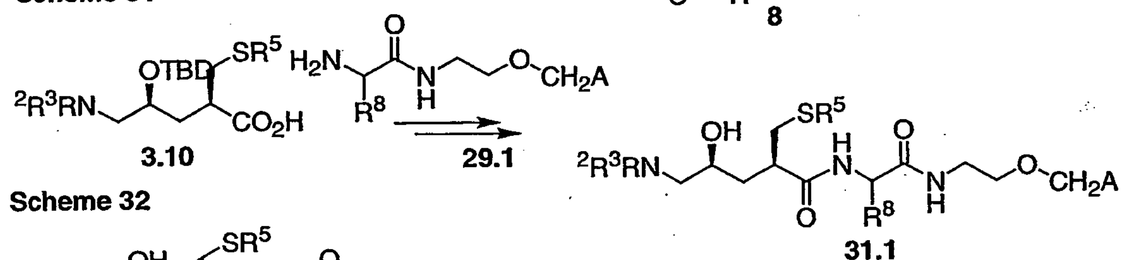
Scheme 29



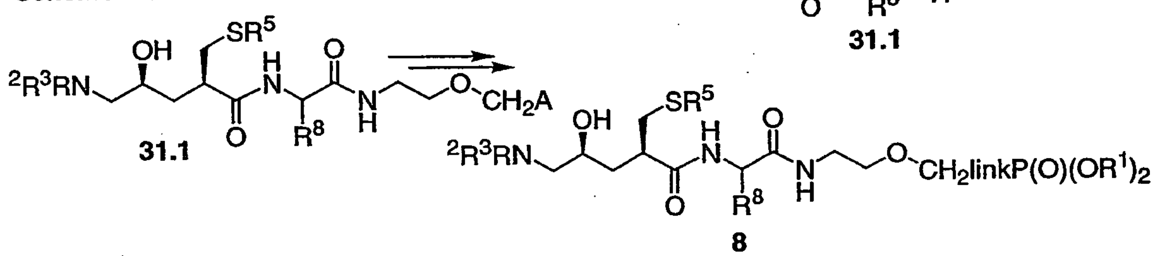
Scheme 30



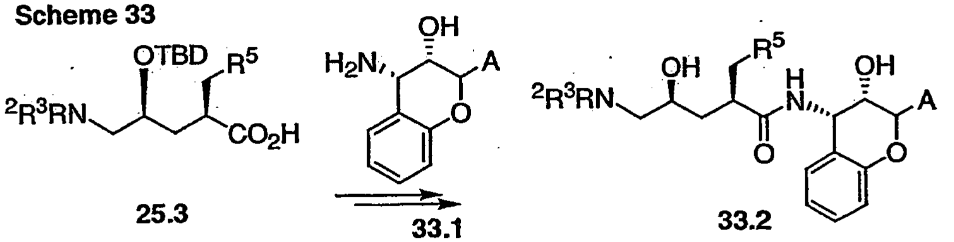
Scheme 31



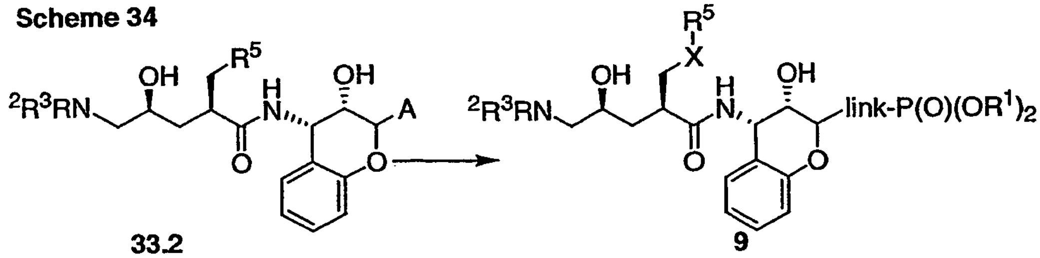
Scheme 32



Scheme 33



Scheme 34



Preparation of the phosphonate ester intermediates 9 in which X is sulfur.

Schemes **35** and **36** illustrate the preparation of the phosphonate esters **9** in which X is sulfur. As shown in Scheme **35**, the carboxylic acid **3.10** is coupled, as described previously, with the chroman amine **33.1** to yield the amide; the product is then desilylated, as described above, to afford the amide **35.1**.

The reactions shown in Scheme **35** illustrate the preparation of the compounds **35.1** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **36** depicts the conversion of the compounds **35.1** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **9** in which X is sulfur. In this procedure, the compounds **35.1** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **9**.

Preparation of the phosphonate ester intermediates 10 in which X is a direct bond.

Schemes **37** and **38** illustrate the preparation of the phosphonate esters **10** in which X is a direct bond. As shown in Scheme **37**, the silylated carboxylic acid **25.3** is coupled, as described above, (Scheme **1**) with the phenylalanine derivative **37.1** to afford the corresponding amide, which upon desilylation produces the hydroxyamide **37.2**. The preparation of the phenylalanine derivatives **37.1** is described in Schemes **182** – **185**.

The reactions shown in Scheme **37** illustrate the preparation of the compounds **37.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **38** depicts the conversion of the compounds **37.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **10** in which X is a direct bond. In this procedure, the compounds **37.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **10**.

Preparation of the phosphonate ester intermediates 10 in which X is sulfur.

Schemes **39** and **40** illustrate the preparation of the phosphonate esters **10** in which X is sulfur. As shown in Scheme **39**, the carboxylic acid **3.10** is coupled, as described previously, with the phenylalanine derivative **37.1** to yield the corresponding amide; the product is then desilylated, as described above, to afford the amide **39.1**.

The reactions shown in Scheme **39** illustrate the preparation of the compounds **39.1** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **40** depicts the conversion of the compounds **39.1** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **10** in which X is sulfur. In this procedure, the compounds **39.1** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **10**.

Preparation of the phosphonate ester intermediates 11 in which X is a direct bond.

Schemes **41** and **42** illustrate the preparation of the phosphonate esters **11** in which X is a direct bond. As shown in Scheme **41**, the silylated carboxylic acid **25.3** is coupled, as described above, (Scheme **1**) with the decahydroisoquinoline carboxamide **41.1**, prepared as described in Scheme **158**, to afford the corresponding amide, which upon desilylation produces the hydroxyamide **41.2**.

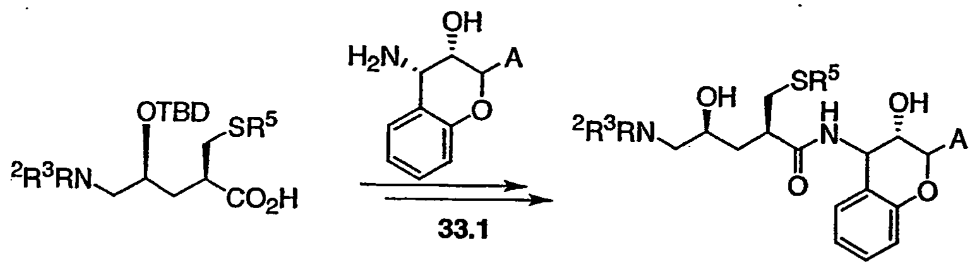
The reactions shown in Scheme **41** illustrate the preparation of the compounds **41.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **42** depicts the conversion of the compounds **41.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **11** in which X is a direct bond. In this procedure, the compounds **41.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compound

Preparation of the phosphonate ester intermediates 11 in which X is sulfur.

Schemes **43** and **44** illustrate the preparation of the phosphonate esters **11** in which X is sulfur. As shown in Scheme **43**, the carboxylic acid **3.10** is coupled, as described previously, with the decahydroisoquinoline carboxamide **41.1** to yield the corresponding amide; the product is then desilylated, as described above, to afford the amide **43.1**.

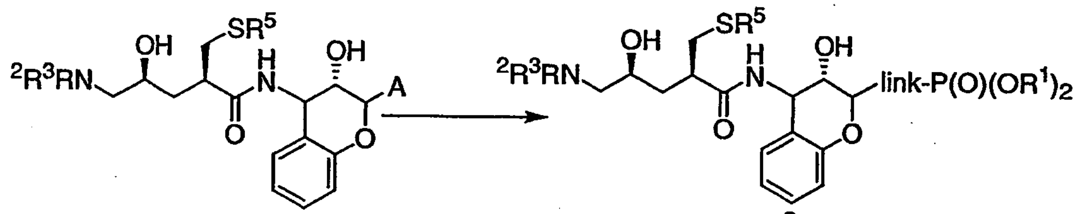
The reactions shown in Scheme **43** illustrate the preparation of the compounds **43.1** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **44** depicts the conversion of the compounds **43.1** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **11** in which X is sulfur. In this procedure, the compounds **43.1** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **11**.

Scheme 35



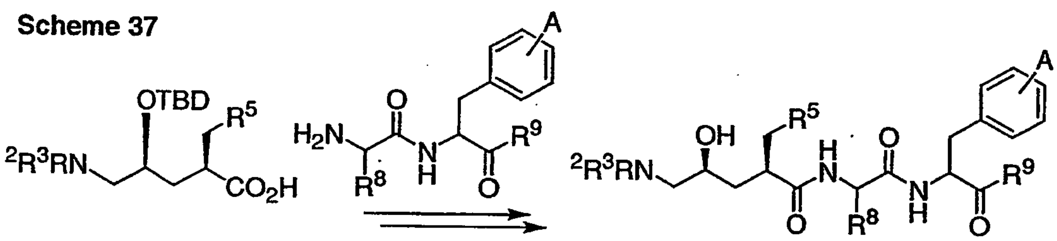
3.10 33.1 35.1

Scheme 36



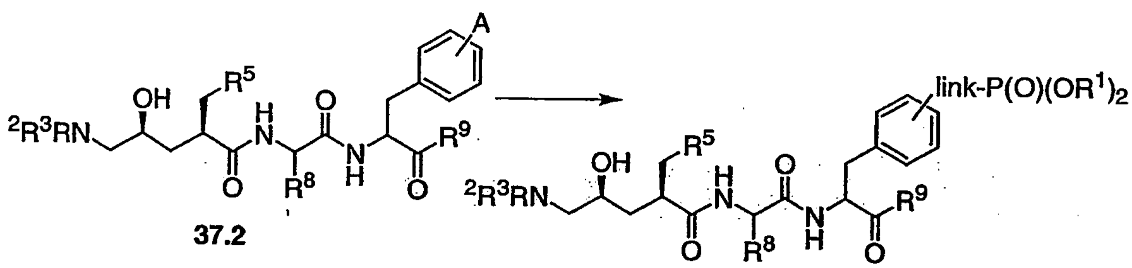
35.1 9

Scheme 37



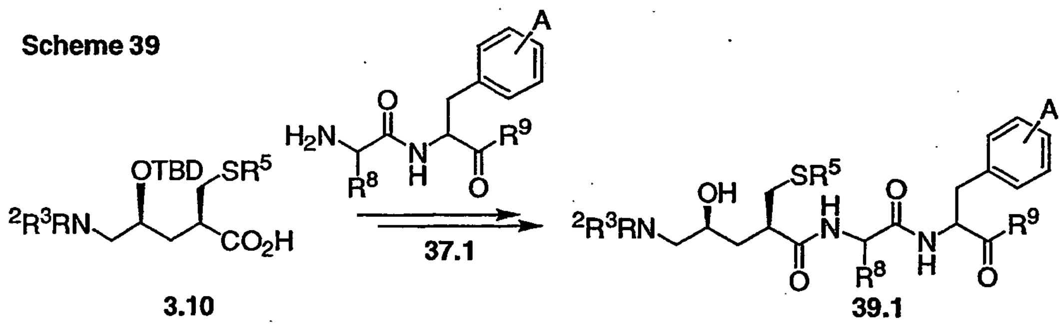
25.3 37.1 37.2

Scheme 38

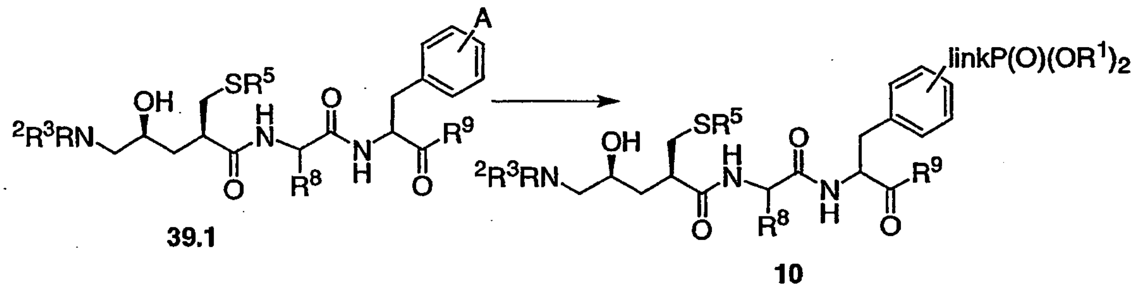


37.2 10

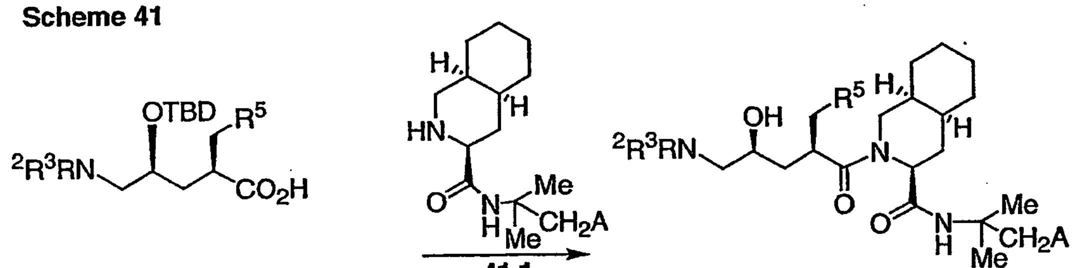
Scheme 39



Scheme 40

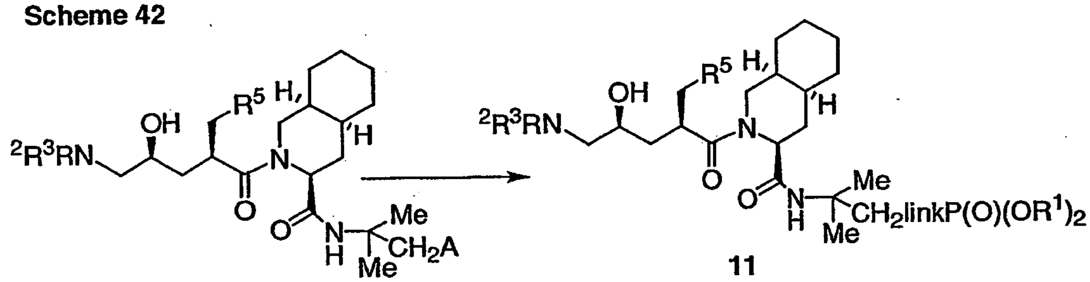


Scheme 41



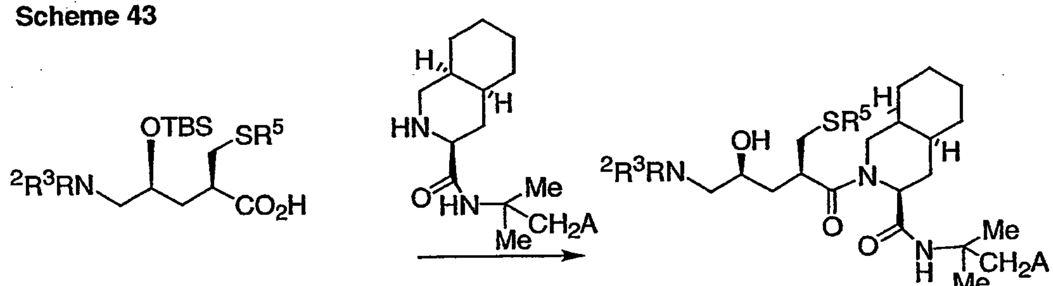
25.3 41.1 41.2

Scheme 42



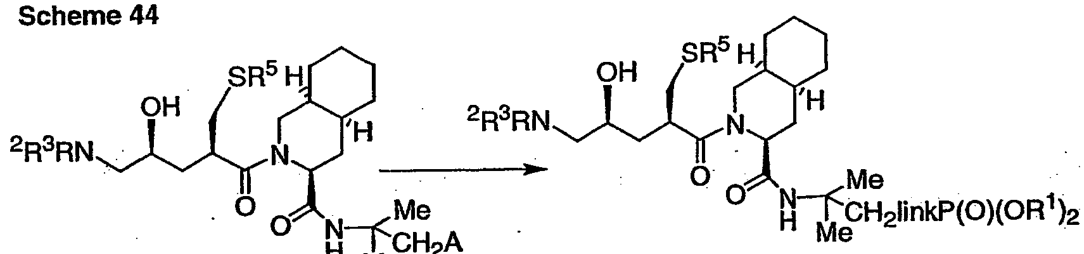
41.2 11

Scheme 43



3.10 41.1 43.1

Scheme 44



43.1 11

Preparation of the phosphonate ester intermediates 12 in which X is a direct bond.

Schemes **45** and **46** illustrate the preparation of the phosphonate esters **12** in which X is a direct bond. As shown in Scheme **45**, the silylated carboxylic acid **25.3** is coupled, as described above, (Scheme **1**) with the decahydroisoquinoline derivative **45.1** to afford the

corresponding amide, which upon desilylation produces the hydroxyamide **45.2**. The preparation of the decahydroisoquinoline derivatives **45.1** is described in Schemes **192 – 197**.

The reactions shown in Scheme **45** illustrate the preparation of the compounds **45.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **46** depicts the conversion of the compounds **45.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **12** in which X is a direct bond. In this procedure, the compounds **45.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **12**.

Preparation of the phosphonate ester intermediates 12 in which X is sulfur.

Schemes **47** and **48** illustrate the preparation of the phosphonate esters **12** in which X is sulfur. As shown in Scheme **47**, the carboxylic acid **3.10** is coupled, as described previously, with the decahydroisoquinoline derivative **45.1** to yield the corresponding amide; the product is then desilylated, as described above, to afford the amide **47.1**.

The reactions shown in Scheme **47** illustrate the preparation of the compounds **47.1** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **48** depicts the conversion of the compounds **47.1** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **12** in which X is sulfur. In this procedure, the compounds **47.1** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **12**.

Preparation of the phosphonate ester intermediates 13 in which X and X' are direct bonds.

Schemes **49** and **50** illustrate the preparation of the phosphonate esters **12** in which X and X' are direct bonds. As shown in Scheme **49**, a BOC-protected aminoacid **49.1** is converted into the corresponding aldehyde **49.2**. A number of methods are known for the conversion of carboxylic acids and derivatives into the corresponding aldehydes, for example as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 619-627. The

conversion is effected by direct reduction of the carboxylic acid, for example employing diisobutyl aluminum hydride, as described in J. Gen. Chem. USSR., 34, 1021, 1964, or alkyl borane reagents, for example as described in J. Org. Chem., 37, 2942, 1972. Alternatively, the carboxylic acid is converted into an amide, such as the N-methoxy N-methyl amide, and the latter compound is reduced with lithium aluminum hydride, for example as described in J. Med. Chem., 1994, 37, 2918, to afford the aldehyde. Alternatively, the carboxylic acid is reduced to the corresponding carbinol which is then oxidized to the aldehyde. The reduction of carboxylic acids to carbinols is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 548ff. The reduction reaction is performed by the use of reducing agents such as borane, as described in J. Am. Chem. Soc., 92, 1637, 1970, or by lithium aluminum hydride, as described in Org. Reac., 6, 649, 1951. The resultant carbinol is then converted into the aldehyde by means of an oxidation reaction. The oxidation of a carbinol to the corresponding aldehyde is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 604ff. The conversion is effected by the use of oxidizing agents such as pyridinium chlorochromate, as described in J.Org. Chem., 50, 262, 1985, or silver carbonate, as described in Compt. Rend. Ser. C., 267, 900, 1968, or dimethyl sulfoxide/acetic anhydride, as described in J. Am. Chem. Soc., 87, 4214, 1965. Preferably, the procedure described in EP 708085 is employed. The carboxylic acid **49.1** is first reacted with equimolar amounts of isobutyl chloroformate and triethylamine in tetrahydrofuran, to afford a mixed anhydride which is then reduced by treatment with sodium borohydride in aqueous tetrahydrofuran at ambient temperature to afford the carbinol **49.2**. The carbinol is then oxidized to the aldehyde **49.3** by reaction with oxalyl chloride and dimethylsulfoxide in dichloromethane at -60°C, as described in EP708085. To transform the aldehyde into the hydroxyester **49.5**, ethyl 3-iodopropionate **49.4** is reacted first with a zinc-copper couple, prepared as described in Org. Syn. Coll. Vol. 5, 855, 1973, and the product is then reacted with trichlorotitanium isopropoxide, as described in EP 708085. The resultant reagent is then treated with the aldehyde **49.3** in dichloromethane at -20°C to yield the hydroxyester **49.5**. The hydroxyester is then cyclized to the lactone **49.6** by treatment with acetic acid in toluene at 100°C, as described in EP 708085. A number of alternative preparations of the lactone **49.6** are known, for example as described in J. Org. Chem., 1985, 50, 4615, J. Org. Chem., 1995, 60, 7927 and J. Org. Chem., 1991, 56, 6500. The lactone **49.6** is then reacted with a substituted benzyl iodide **49.7** to afford the alkylated product **49.8**.

The preparation of the benzyl halides **49.7** is described below, (Schemes **165** – **169**). The alkylation reaction is performed in an aprotic organic solvent such as dimethylformamide or tetrahydrofuran, in the presence of a strong base such as sodium hydride or lithium hexamethyl disilylazide. Preferably, the lactone is first reacted with lithium bis(trimethylsilyl)amide in a mixture of tetrahydrofuran and 1,3-dimethyltetrahydropyrimidinone, and then ethyl 3-iodopropioinate is added, as described in EP 708085, to prepare the alkylated lactone **49.8**. The lactone is then converted into the corresponding hydroxyacid **49.9** by alkaline hydrolysis, for example by treatment with lithium hydroxide in aqueous dimethoxyethane, as described in EP 708085. The hydroxyacid is then converted into the tert. butyldimethylsilyl ether **49.10**, by reaction with excess chloro tert. butyldimethylsilane and imidazole in dimethylformamide, followed by alkaline hydrolysis, employing potassium carbonate in aqueous methanolic tetrahydrofuran, as described in EP 708085, to yield the silyl ether **49.10**. The carboxylic acid is then coupled, as described above (Scheme **5**) with the amine R^2R^3NH to afford the amide product **49.11**. The BOC protecting group is then removed to give the free amine **49.12**. The removal of BOC protecting groups is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 328. The deprotection can be effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride or trifluoroacetic acid, or by reaction with trimethylsilyl iodide or aluminum chloride. Preferably, the BOC protecting group is removed by treatment of the substrate with 3M hydrogen chloride in ethyl acetate, as described in J. Org. Chem., 43, 2285, 1978, a procedure which also removes the silyl protecting group to afford the hydroxy amine **49.12**. The latter compound is then coupled with the carboxylic acid $R^{10}COOH$, or a functional equivalent thereof, to give the amide or carbamate product **49.13**. The preparation of amides by the reaction between amines and amides is described above (Scheme **1**). Compounds in which the group R^{10} is alkoxy are carbamates; the preparation of carbamates is described below (Scheme **198**)

The reactions shown in Scheme **49** illustrate the preparation of the compounds **49.13** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **50** depicts the conversion of the compounds **49.13** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **13** in which X and X' are direct bonds. In this procedure, the compounds **49.13** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **13**.

Preparation of the phosphonate ester intermediates 13 in which X is a direct bond and X' is sulfur.

Schemes **51** and **52** illustrate the preparation of the phosphonate esters **13** in which X is a direct bond and X' is sulfur. In this procedure, BOC serine methyl ester mesylate, **51.1**, the preparation of which is described in Synlett., 1997, 169, is reacted with the thiol **51.2**, employing the conditions described in Scheme **3**, to prepare the thioether **51.3**. The methyl ester group is then transformed into the corresponding aldehyde **51.4**. The reduction of esters to aldehydes is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 621. The conversion is effected by treatment with diisobutyl aluminum hydride, sodium aluminum hydride, lithium tri-tertiary butoxy aluminum hydride and the like. Preferably, the ester **51.3** is reduced to the aldehyde **51.4** by reaction with the stoichiometric amount of diisobutyl aluminum hydride in toluene at -80°C, as described in Syn., 617, 1975. The aldehyde is then transformed into the diamide **51.5**, using the sequence of reactions and reaction conditions described above (Scheme **49**) for the conversion of the aldehyde **49.3** into the diamide **49.13**.

The reactions shown in Scheme **51** illustrate the preparation of the compounds **51.5** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **52** depicts the conversion of the compounds **51.5** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **13** in which X is a direct bond and X' is sulfur. In this procedure, the compounds **51.5** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **13**.

Preparation of the phosphonate ester intermediates 13 in which X and X' are sulfur.

Schemes **53**, **54** and **55** illustrate the preparation of the phosphonate esters **13** in which X and X' are sulfur. As shown in Scheme **53**, the aldehyde **51.4** is reacted with the dianion of N-methylmethacrylamide **53.1** to form the hydroxyamide **53.2**. The dianion is generated by treatment of N-methylmethacrylamide with two equivalents of an alkyllithium, for example n-butyllithium, in an organic solvent such as tetrahydrofuran or dimethoxyethane, as described in J. Org. Chem., 1986, 51, 3921. The dianion is then reacted with the aldehyde in the presence

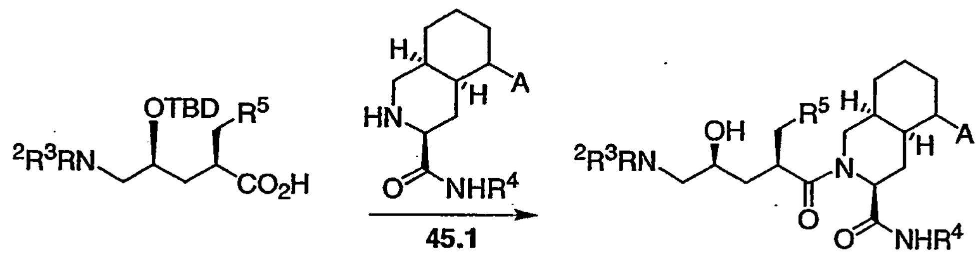
of chlorotitanium triisopropoxide, to afford the olefinic amide **53.2**. The product is cyclized to produce the methylene lactone **53.3** by heating in an inert solvent such as xylene, at reflux temperature, as described in J. Org. Chem., 1986, 51, 3921. The methylene lactone is then reacted with the thiol **53.4** to yield the thioether **53.5**. The preparation of the thiols **53.4** is described below, (Schemes **170 – 173**). The addition of thiols to methylene lactones analogous to the compound **53.3** is described in J. Org. Chem., 1986, 51, 3921. Equimolar amounts of the reactants are combined in an alcoholic solvent such as methanol at about 60°C, in the presence of a tertiary base such as triethylamine, to give the addition product **53.5**. The latter compound is then subjected to basic hydrolysis, for example by reaction with lithium hydroxide, as described above, (Scheme **49**) to produce the hydroxyacid **53.6**. The product is silylated, as described in Scheme **49**, to give the silylated carbinol **53.7**, and the product is then converted, as described in Scheme **49**, into the diamide **53.8**.

Scheme **54** illustrates an alternative method for the preparation of the diamides **53.8**. In this procedure, the anion of the lactone **54.1**, obtained as an intermediate in the conversion of the aldehyde **51.4** into the diamide **51.5**, (Scheme **51**) is reacted with formaldehyde or a functional equivalent thereof, to afford the hydroxymethyl compound **54.2**. The generation of the anion of lactones analogous to **54.1**, and alkylation thereof, is described above in Scheme **49**. Preferably, the anion is prepared by reaction of the lactone, in a solvent mixture composed of tetrahydrofuran and 1,3-dimethyltetrahydropyrimidinone, with lithium bis(trimethylsilyl)amide, as described in EP 708085, and formaldehyde, generated by pyrolysis of paraformaldehyde, is then introduced in an inert gas stream. The hydroxymethyl product is then converted into the corresponding mesylate **54.3**, by reaction with methanesulfonyl chloride in dichloromethane containing a tertiary base such as triethylamine or dimethylaminopyridine, and the mesylate is then reacted with the thiol reagent **53.4**, using the procedure described above for the preparation of the thioether **51.3**, to yield the thioether **53.5**. The product is then transformed, as described above, into the diamide **53.8**.

The reactions shown in Schemes **53** and **54** illustrate the preparation of the compounds **53.8** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **55** depicts the conversion of the compounds **53.8** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **13** in which X and X' are sulfur. In this

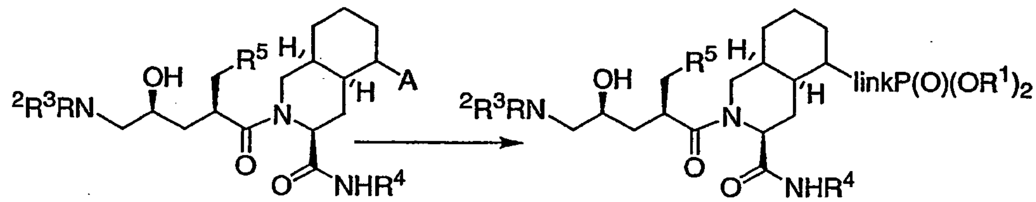
procedure, the compounds **53.8** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **13.**

Scheme 45



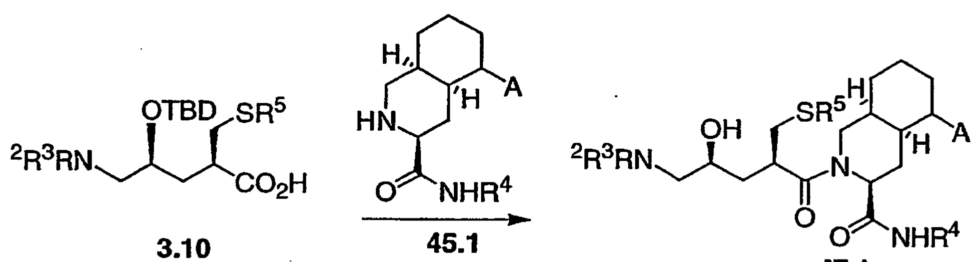
25.3 45.2

Scheme 46



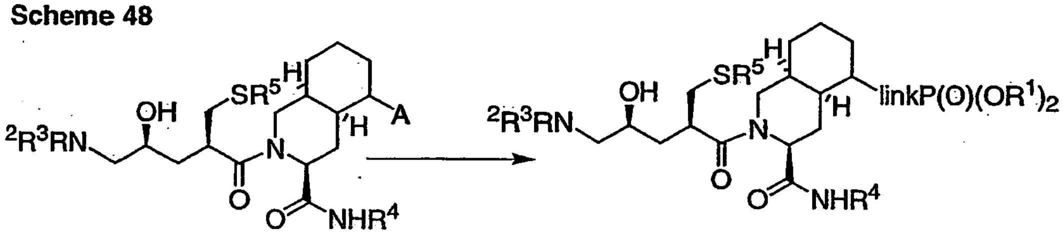
45.2 12

Scheme 47



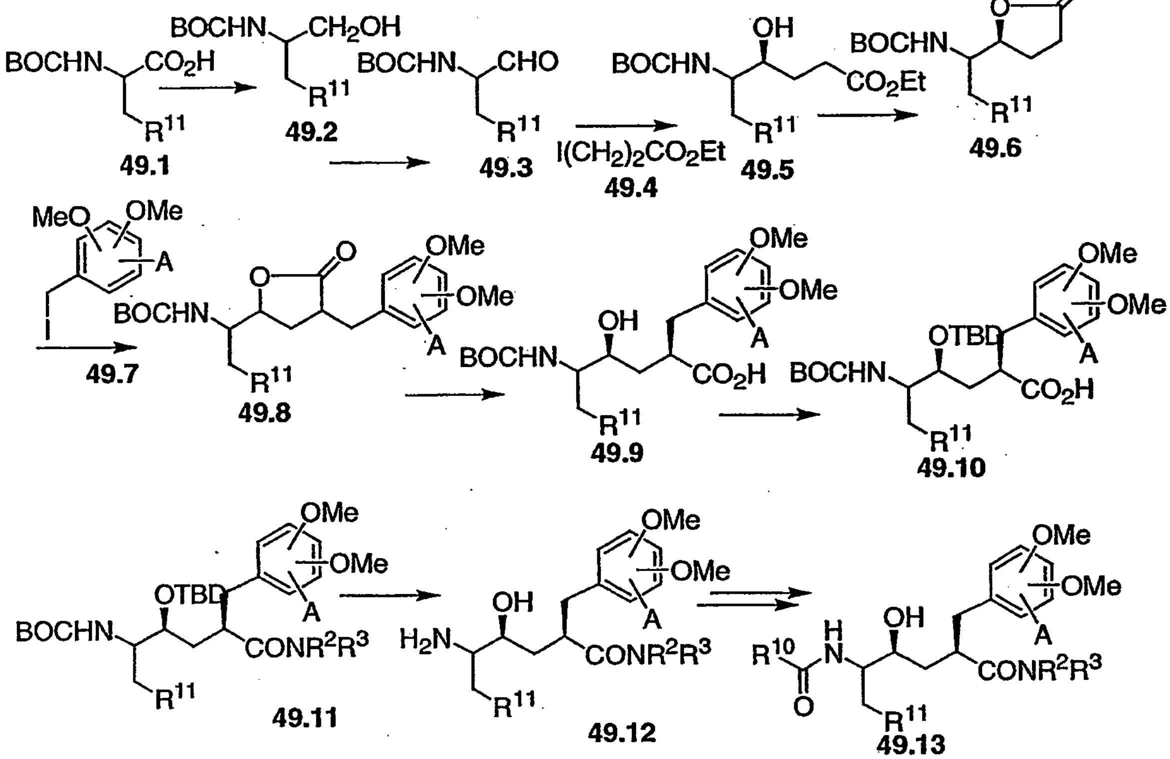
3.10 47.1

Scheme 48

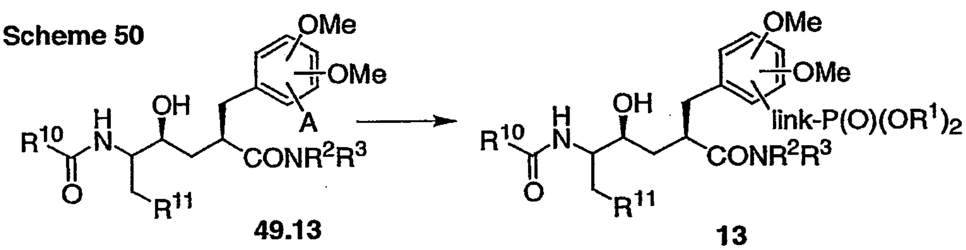


47.1 12

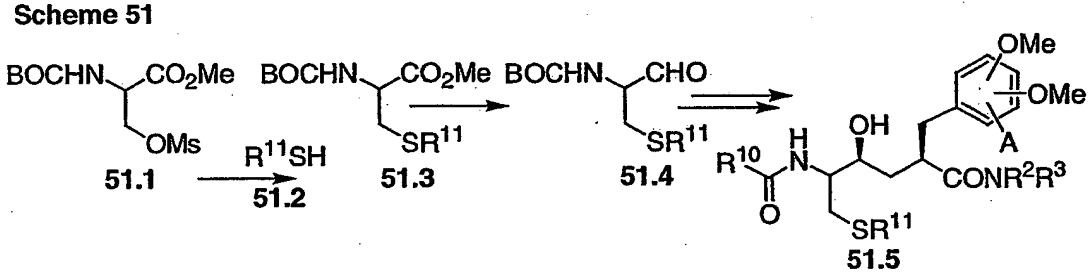
Scheme 49



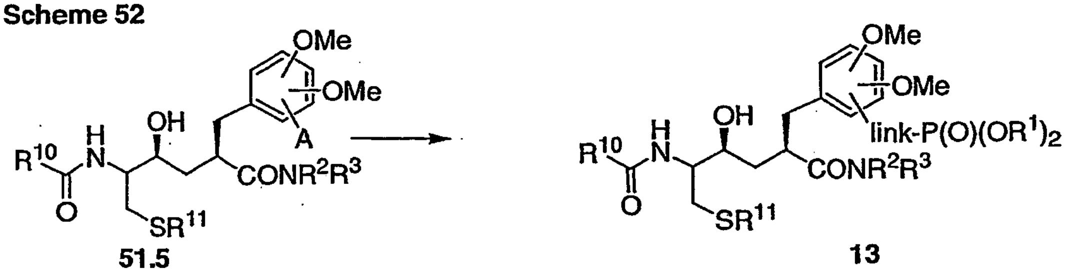
Scheme 50



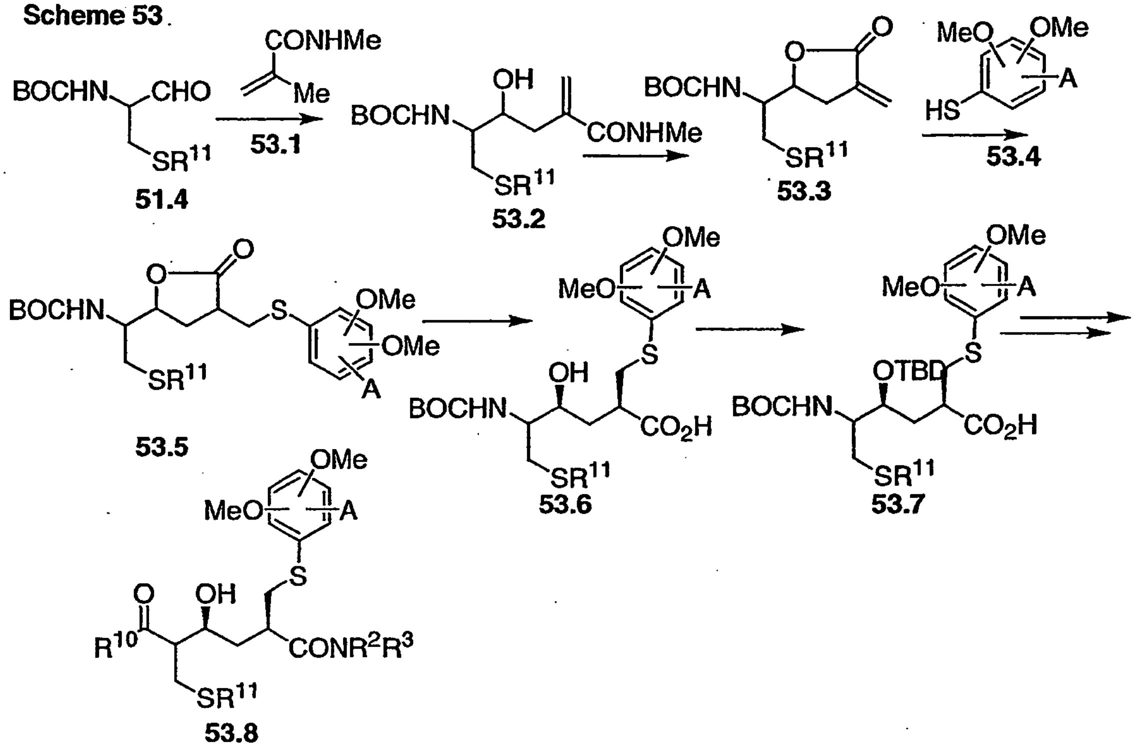
Scheme 51



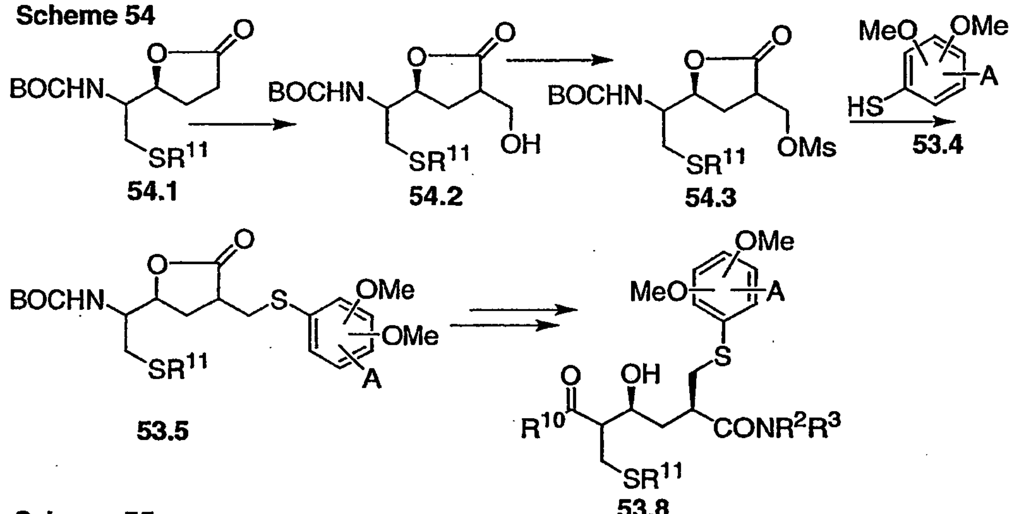
Scheme 52



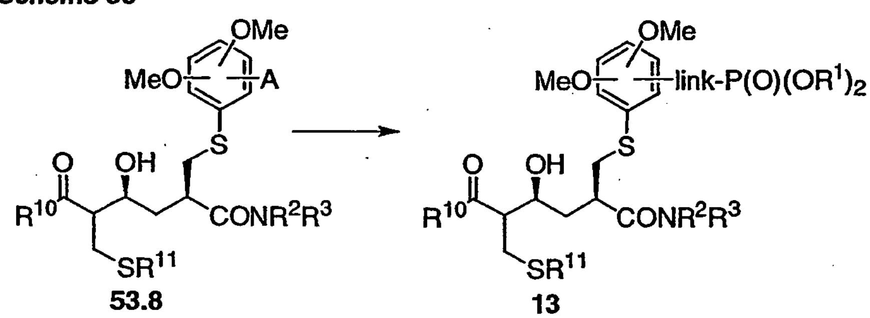
Scheme 53



Scheme 54



Scheme 55



Preparation of the phosphonate ester intermediates 13 in which X is sulfur and X' is a direct bond.

Schemes **56** and **57** illustrate the preparation of the phosphonate esters **13** in which X is sulfur and X' is a direct bond. In this procedure, the BOC-protected aldehyde **49.3** is converted, as described in Scheme **53**, into the methylene lactone **56.1**. The lactone is then reacted with the thiol **53.4** and a base, as described in Scheme **53**, to yield the thioether **56.2**. The thioether is then transformed, as described in Scheme **53**, into the diamide **56.3**.

The reactions shown in Scheme **56** illustrate the preparation of the compounds **56.3** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **57** depicts the conversion of the compounds **56.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **13** in which X is sulfur and X' is a direct bond. In this procedure, the compounds **56.3** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **13**.

Preparation of the phosphonate ester intermediates 14 in which X and X' are direct bonds.

Schemes **58** and **59** illustrate the preparation of the phosphonate esters **14** in which X and X' are direct bonds. In this procedure, the lactone **49.6** is reacted, as described in Scheme **49**, with a substituted benzyl iodide **58.1**, to produce the alkylated compound **58.2**. The preparation of the benzyl iodides **58.1** is described in Schemes **187** - **191**. The product is then transformed, as described in Scheme **49**, into the diamide **58.3**.

The reactions shown in Scheme **58** illustrate the preparation of the compounds **58.3** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **59** depicts the conversion of the compounds **58.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **14** in which X and X' are direct bonds. In this procedure, the compounds **58.3** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **14**.

Preparation of the phosphonate ester intermediates 14 in which X is a direct bond and X' is sulfur.

Schemes **60** and **61** illustrate the preparation of the phosphonate esters **14** in which X is a direct bond and X' is sulfur. In this procedure, the lactone **54.1** is reacted, as described in Scheme **49**, with a substituted benzyl iodide **58.1**, to produce the alkylated compound **60.1**. The product is then transformed, as described in Scheme **49**, into the diamide **60.2**.

The reactions shown in Scheme **60** illustrate the preparation of the compounds **60.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **61** depicts the conversion of the compounds **60.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **14** in which X is a direct bond and X' is sulfur. In this procedure, the compounds **60.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **14**.

Preparation of the phosphonate ester intermediates 14 in which X and X' are sulfur.

Schemes **62**, **63** and **64** illustrate the preparation of the phosphonate esters **14** in which X and X' are sulfur. As shown in Scheme **62**, the methylene lactone **53.3** is reacted, as described in Scheme **53**, with a substituted thiophenol **62.1** to produce the addition product **62.2**. The preparation of the substituted thiophenols **62.1** is described below, (Schemes **144 – 153**). The product is then transformed, as described in Scheme **53**, into the diamide **62.3**.

Scheme **63** illustrates an alternative method for the preparation of the diamide **62.3**. In this procedure, the mesylate **54.3** is reacted, as described in Scheme **54**, with the thiol **62.1** to afford the alkylation product **63.1**. The product is then transformed, as described in Scheme **53**, into the diamide **62.3**.

The reactions shown in Schemes **62** and **63** illustrate the preparation of the compounds **62.3** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **64** depicts the conversion of the compounds **62.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **14** in which X and X' are sulfur. In this procedure, the compounds **62.3** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **14**.

Preparation of the phosphonate ester intermediates 14 in which X is sulfur and X' is a direct bond.

Schemes **65** and **66** illustrate the preparation of the phosphonate esters **14** in which X is sulfur and X' is a direct bond. In this procedure, the methylene lactone **56.1** is reacted, as described in Scheme **53**, with a substituted thiophenol **62.1**, to produce the thioether **65.1**. The product is then transformed, as described in Scheme **53**, into the diamide **65.2**.

The reactions shown in Scheme **65** illustrate the preparation of the compounds **65.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **66** depicts the conversion of the compounds **65.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **14** in which X is sulfur and X' is a direct bond. In this procedure, the compounds **65.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **14**.

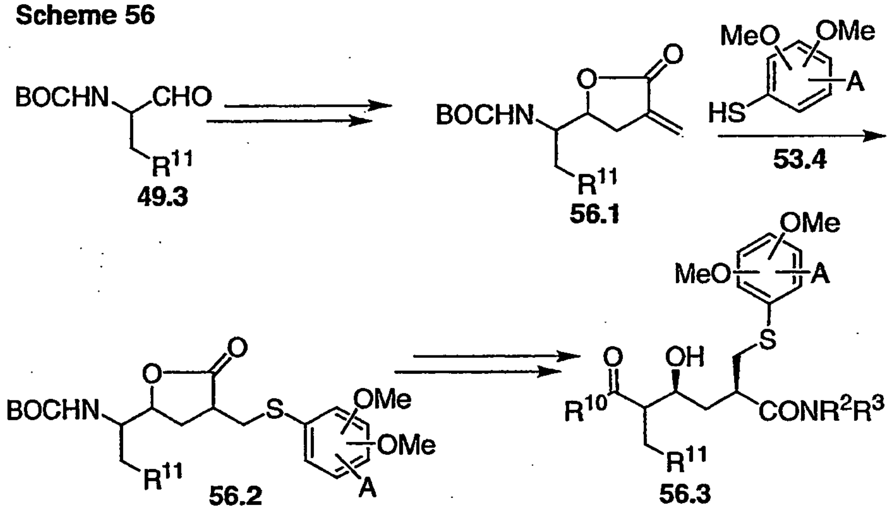
Preparation of the phosphonate ester intermediates 15 in which X and X' are direct bonds.

Schemes **67** and **68** illustrate the preparation of the phosphonate esters **15** in which X and X' are direct bonds. In this procedure, the BOC-protected phenylalanine derivative **67.1** is converted into the corresponding aldehyde **67.2**, using the procedures described above (Scheme **49**). The preparation of the phenylalanine derivatives **67.1** is described below, (Schemes **182** – **184**). The aldehyde is then converted, using the procedures described in Scheme **49**, into the lactone **67.3**. The latter compound is then alkylated, as described in Scheme **49**, with the reagent R^5CH_2I, (**67.4**), to afford the alkylated product **67.5**. This compound is then converted, as described in Scheme **49**, into the diamide **67.6**.

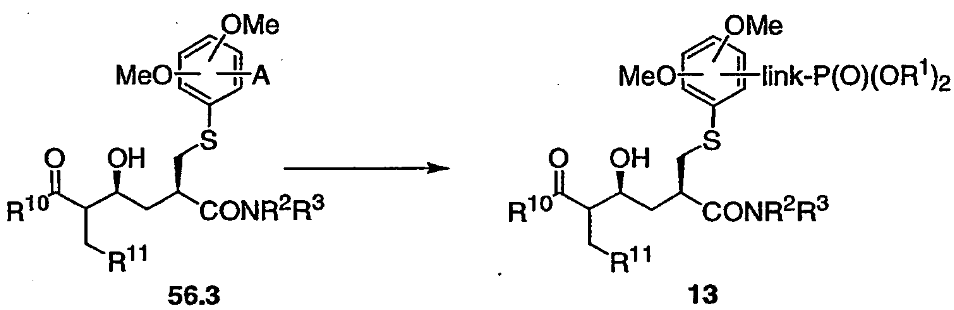
The reactions shown in Scheme **67** illustrate the preparation of the compounds **67.6** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **68** depicts the conversion of the compounds **67.6** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **15** in which X and X' are direct bonds. In this

procedure, the compounds **67.6** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **15**.

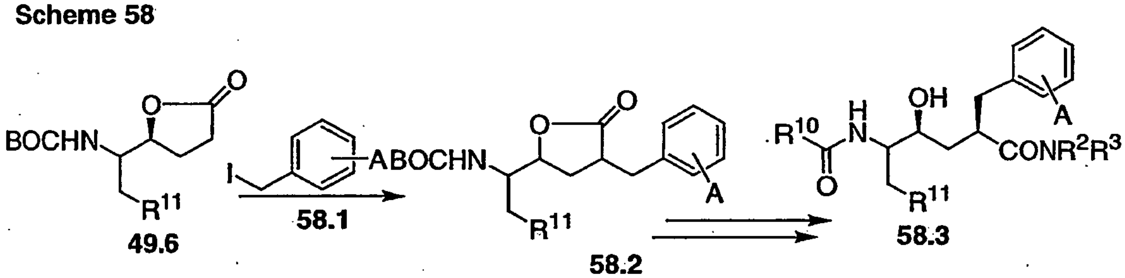
Scheme 56



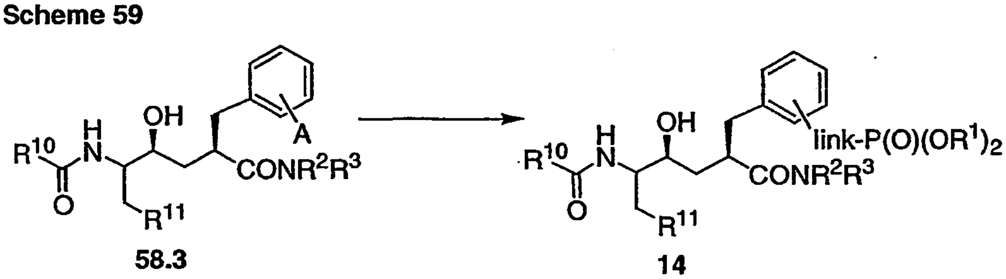
Scheme 57



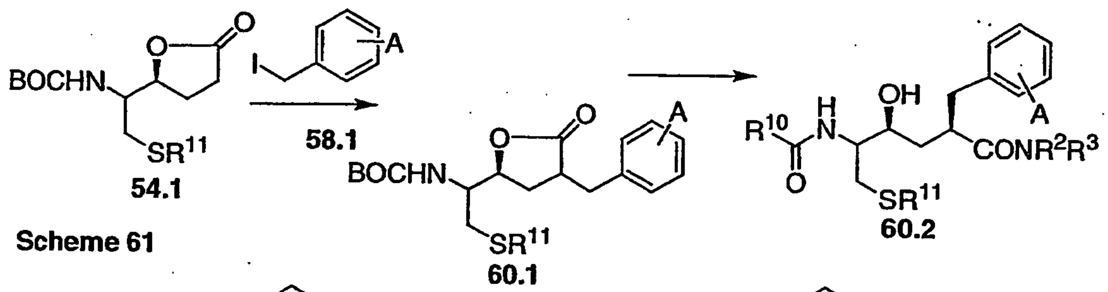
Scheme 58



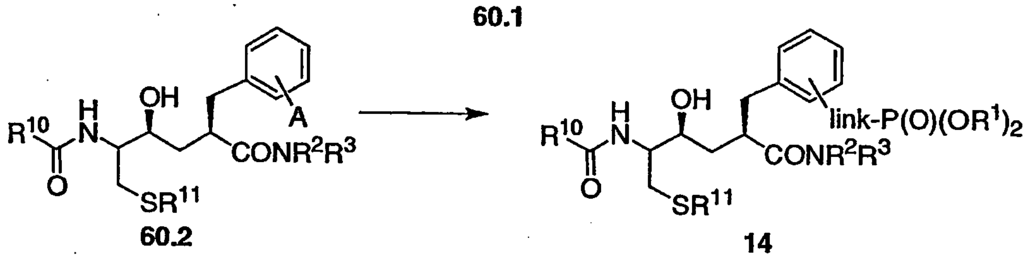
Scheme 59



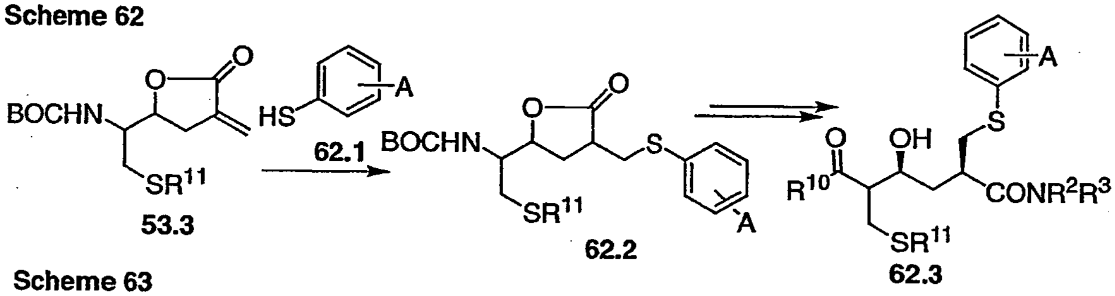
Scheme 60



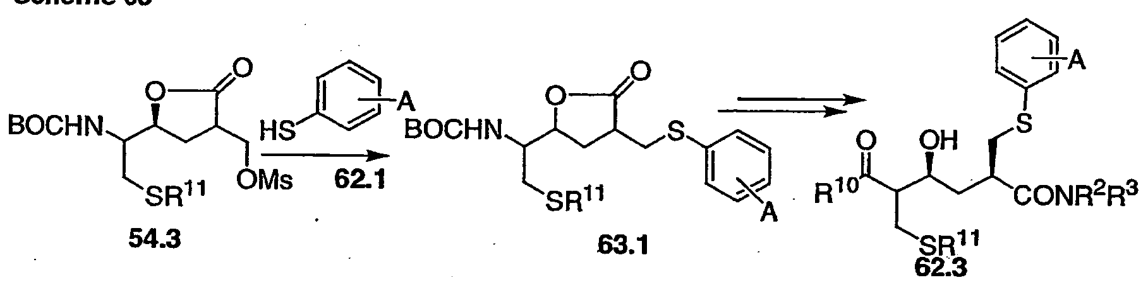
Scheme 61



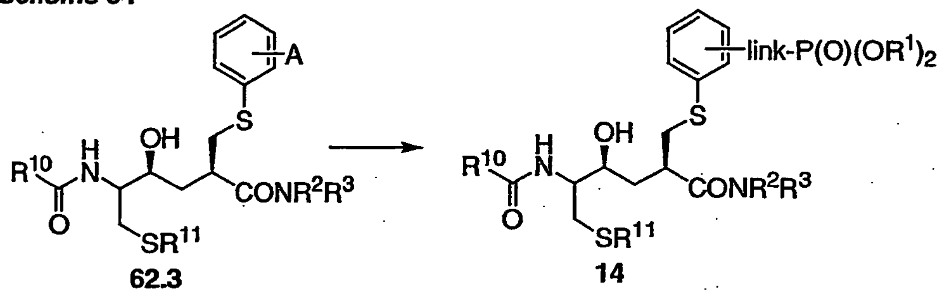
Scheme 62



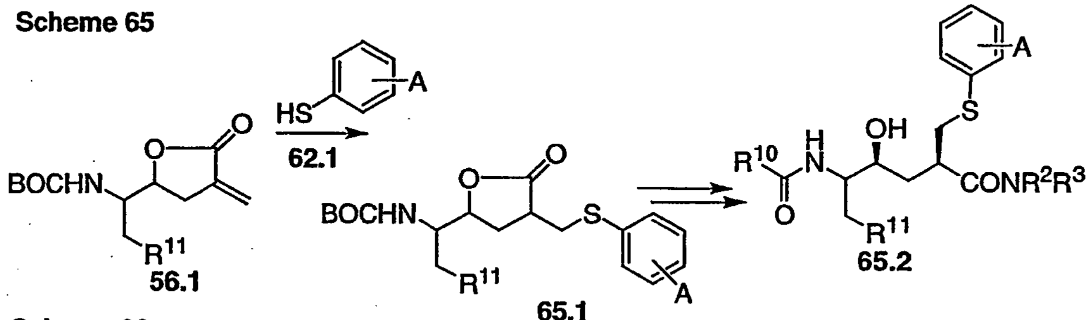
Scheme 63



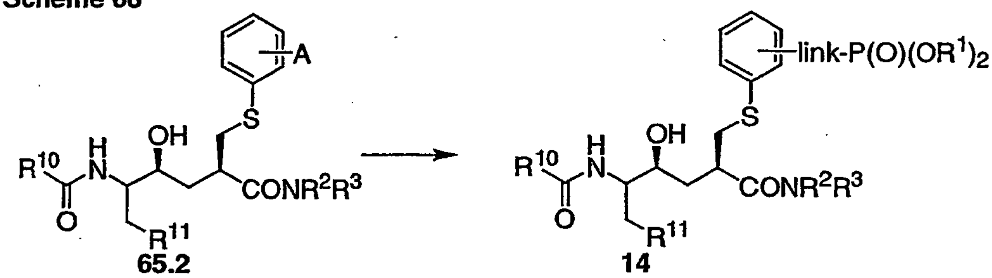
Scheme 64



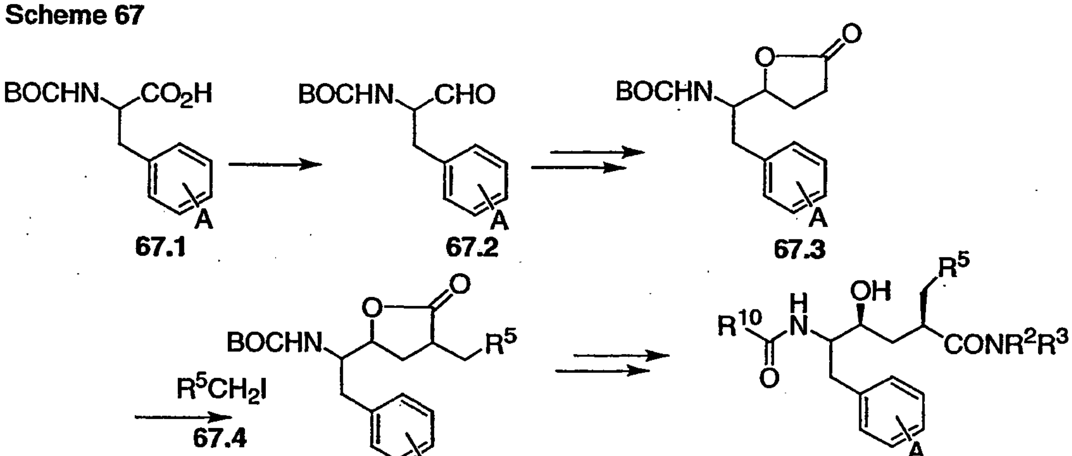
Scheme 65



Scheme 66

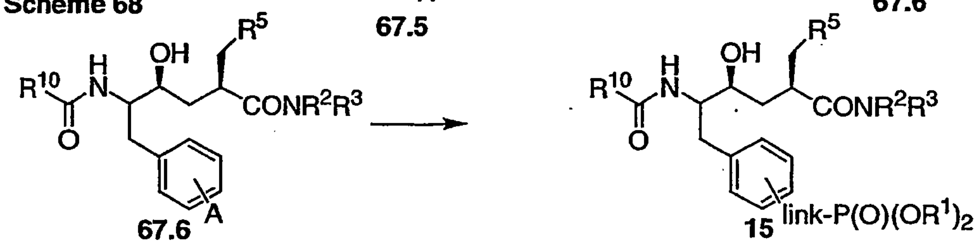


Scheme 67



67.5 67.6

Scheme 68



Preparation of the phosphonate ester intermediates 15 in which X is a direct bond and X' is sulfur.

Schemes **69** and **70** illustrate the preparation of the phosphonate esters **15** in which X is a direct bond and X' is sulfur. In this procedure, the mesylate **51.1** is reacted, as described in Scheme **51**, with the thiophenol derivative **69.1**. The preparation of the thiophenol derivatives **69.1** is described below, Schemes **144 – 153**. The product is then converted, as described in Scheme **51**, into the corresponding aldehyde **69.3**, and the latter compound is then transformed, as described in Scheme **49**, into the lactone **69.4**. The lactone is then alkylated, as described in Scheme **49**, with the reagent R^5CH_2I, (**67.4**), to afford the alkylated product **69.5**. This compound is then converted, as described in Scheme **49**, into the diamide **69.6**.

The reactions shown in Scheme **69** illustrate the preparation of the compounds **69.6** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **70** depicts the conversion of the compounds **69.6** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **15** in which X is a direct bond and X' is sulfur. In this procedure, the compounds **69.6** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **15**.

Preparation of the phosphonate ester intermediates 15 in which X and X' are sulfur.

Schemes **71**, **72** and **73** illustrate the preparation of the phosphonate esters **15** in which X and X' are sulfur. As shown in Scheme **71**, the aldehyde **69.3** is converted, as described in Scheme **53**, into the methylene lactone **71.1**. The lactone is then reacted, as described in Scheme **53**, with the thiol reagent **71.2** to yield the thioether product **71.3**. The product is then transformed, as described in Scheme **53**, into the diamide **71.4**.

Scheme **72** illustrates an alternative method for the preparation of the diamide **71.4**. In this procedure, the lactone **69.4** is reacted, as described in Scheme **54**, with formaldehyde or a formaldehyde equivalent, to afford the hydroxymethyl product **72.1**. The product is then transformed, by mesylation followed by reaction of the mesylate with the thiol reagent **71.2**, using the procedures described in Scheme **53**, into the thioether **71.3**.The latter compound is then converted, as described in Scheme **53**, into the diamide **71.4**.

The reactions shown in Schemes **71** and **72** illustrate the preparation of the compounds **71.4** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **73** depicts the conversion of the compounds **71.4** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **15** in which X and X' are sulfur. In this procedure, the compounds **71.4** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **15**.

Preparation of the phosphonate ester intermediates 15 in which X is sulfur and X' is a direct bond.

Schemes **74** and **75** illustrate the preparation of the phosphonate esters **15** in which X is sulfur and X' is a direct bond. In this procedure, the aldehyde **67.2** is converted, as described in Scheme **53**, into the methylene lactone **74.1**. The lactone is then reacted, as described in Scheme **53**, with the thiol **71.2** to afford the thioether **74.2**. This compound is then converted, as described in Scheme **53**, into the diamide **74.3**.

The reactions shown in Schemes **74** illustrate the preparation of the compounds **74.3** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **75** depicts the conversion of the compounds **74.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **15** in which X is sulfur and X' is a direct bond. In this procedure, the compounds **74.3** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **15**.

Preparation of the phosphonate ester intermediates 16 in which X and X' are direct bonds.

Schemes **76** and **77** illustrate the preparation of the phosphonate esters **16** in which X and X' are direct bonds. In this procedure, the lactone **49.6** is reacted, as described in Scheme **49**, with the iodo compound **67.4** to yield the alkylated lactone **76.1**. The lactone is then converted, as described in Scheme **49**, into the carboxylic acid **76.2**. The carboxylic acid is then coupled, as described in Scheme **1**, with the aminoindanol derivative **1.2** to afford the amide **76.3**. The latter compound is then converted, as described in Scheme **49**, into the diamide **76.4**.

The reactions shown in Scheme **76** illustrate the preparation of the compounds **76.4** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **77** depicts the conversion of the compounds **76.4** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **16** in which X and X' are direct bonds. In this procedure, the compounds **76.4** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **16**.

Preparation of the phosphonate ester intermediates 16 in which X is a direct bond and X' is sulfur.

Schemes **78** and **79** illustrate the preparation of the phosphonate esters **16** in which X is a direct bond and X' is sulfur. In this procedure, the lactone **54.1** is reacted, as described in Scheme **49**, with the iodo compound **67.4**, to produce the alkylated compound **78.1**. This material is then transformed, as described in Scheme **49**, into the carboxylic acid **78.2**, which is then transformed, as described in Scheme **76**, into the diamide **78.3**.

The reactions shown in Scheme **78** illustrate the preparation of the compounds **78.3** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **79** depicts the conversion of the compounds **78.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **16** in which X is a direct bond and X' is sulfur. In this procedure, the compounds **78.3** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **16**.

Preparation of the phosphonate ester intermediates 16 in which X and X' are sulfur.

Schemes **80, 81** and **82** illustrate the preparation of the phosphonate esters **15** in which X and X' are sulfur. As shown in Scheme **80**, the methylene lactone **53.3** is reacted with the thiol **71.2** to produce the thioether **80.1**. The compound is then transformed, as described in Scheme **49**, into the silyl-protected carboxylic acid **80.2**. This material is then converted, as described in Scheme **76**, into the diamide **80.3**.

Scheme **81** illustrates an alternative method for the preparation of the compounds **80.2**. In this procedure, the mesylate **54.3** is reacted, as described in Scheme **54**, with the thiol **71.2**, to

prepare the thioether **80.1**. The product is then transformed, as described in Scheme **54**, into the diamide **80.3**.

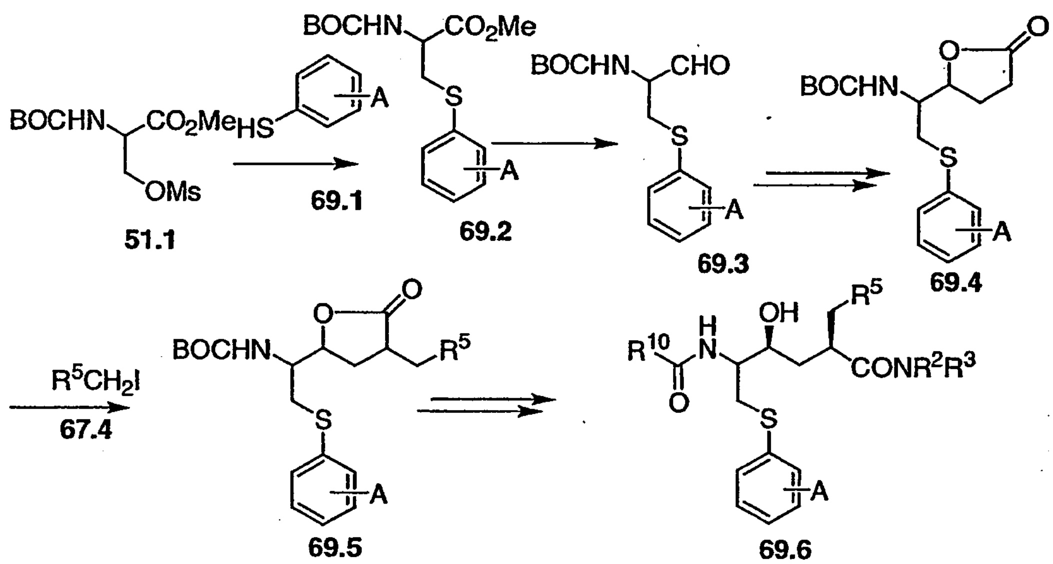
The reactions shown in Schemes **80** and **81** illustrate the preparation of the compounds **80.3** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **82** depicts the conversion of the compounds **80.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **16** in which X and X' are sulfur. In this procedure, the compounds **80.3** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **16**.

Preparation of the phosphonate ester intermediates 16 in which X is sulfur and X' is a direct bond.

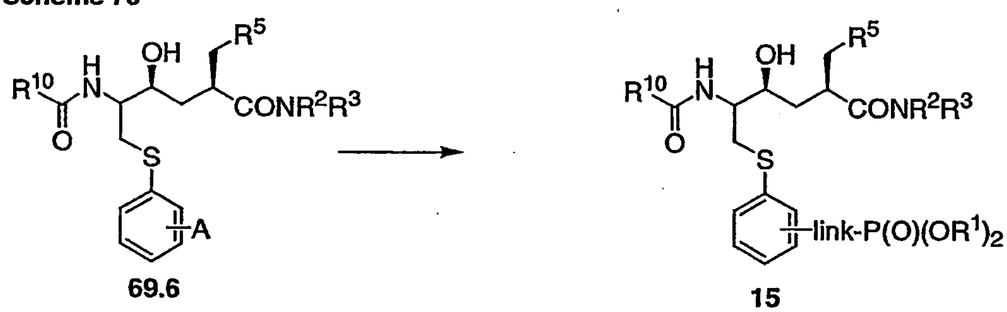
Schemes **83** and **84** illustrate the preparation of the phosphonate esters **16** in which X is sulfur and X' is a direct bond. In this procedure, the methylene lactone **53.3** is reacted, as described in Scheme **53**, with the thiol **71.2** to yield the thioether **83.1**. The product is then converted, as described in Scheme **76**, into the diamide **83.2**.

The reactions shown in Scheme **83** illustrate the preparation of the compounds **83.2** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **84** depicts the conversion of the compounds **83.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **16** in which X is sulfur and X' is a direct bond. In this procedure, the compounds **83.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **16**.

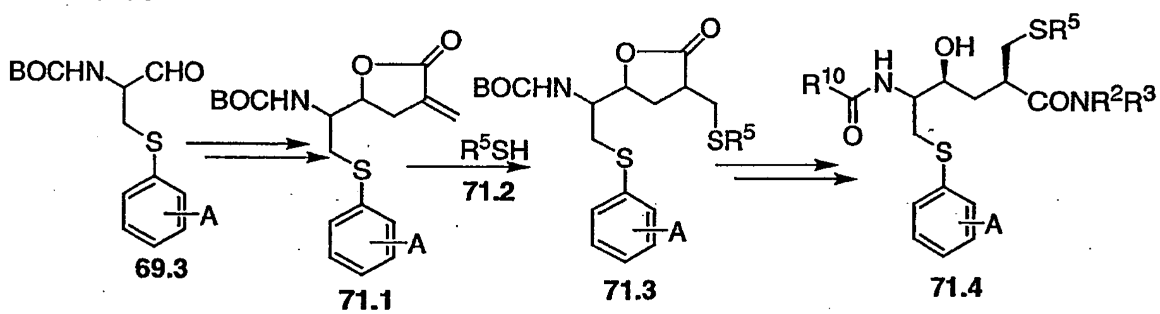
Scheme 69



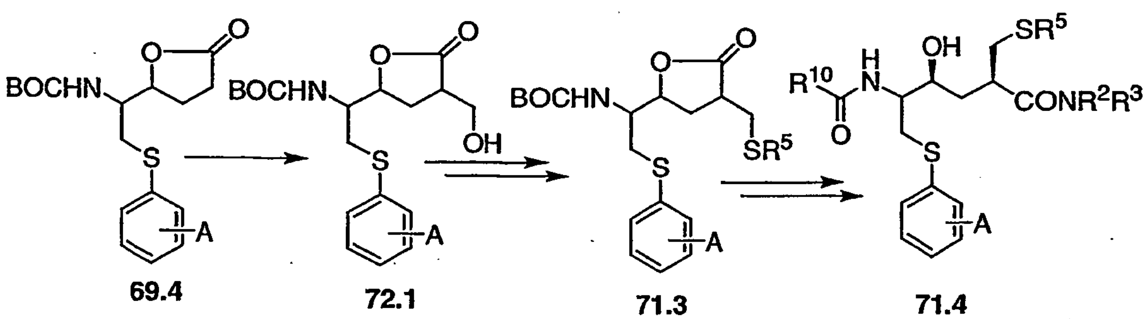
Scheme 70



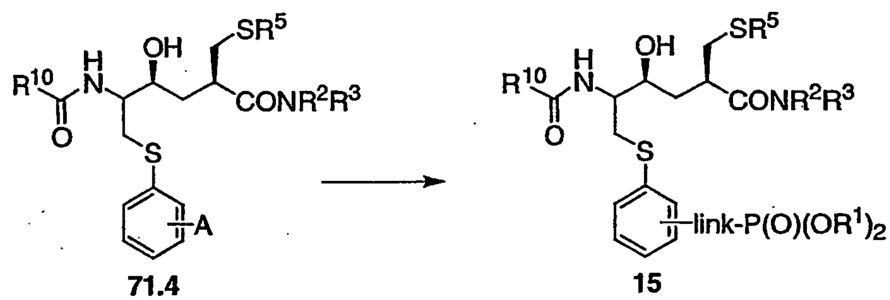
Scheme 71



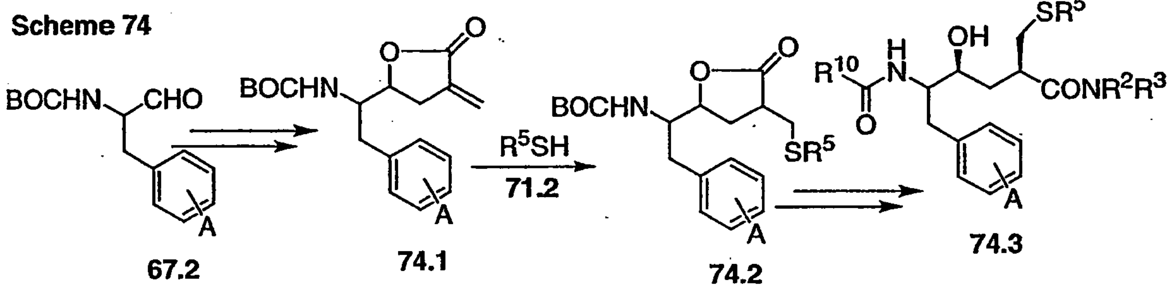
Scheme 72



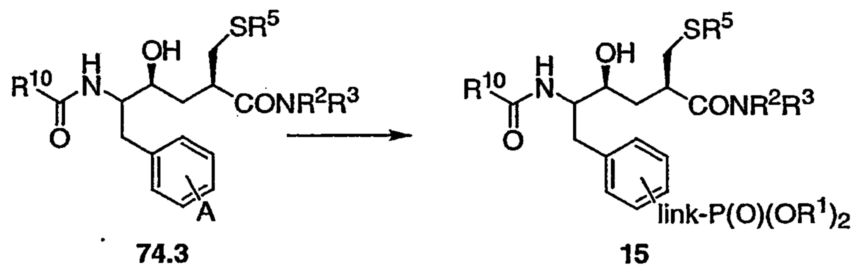
Scheme 73



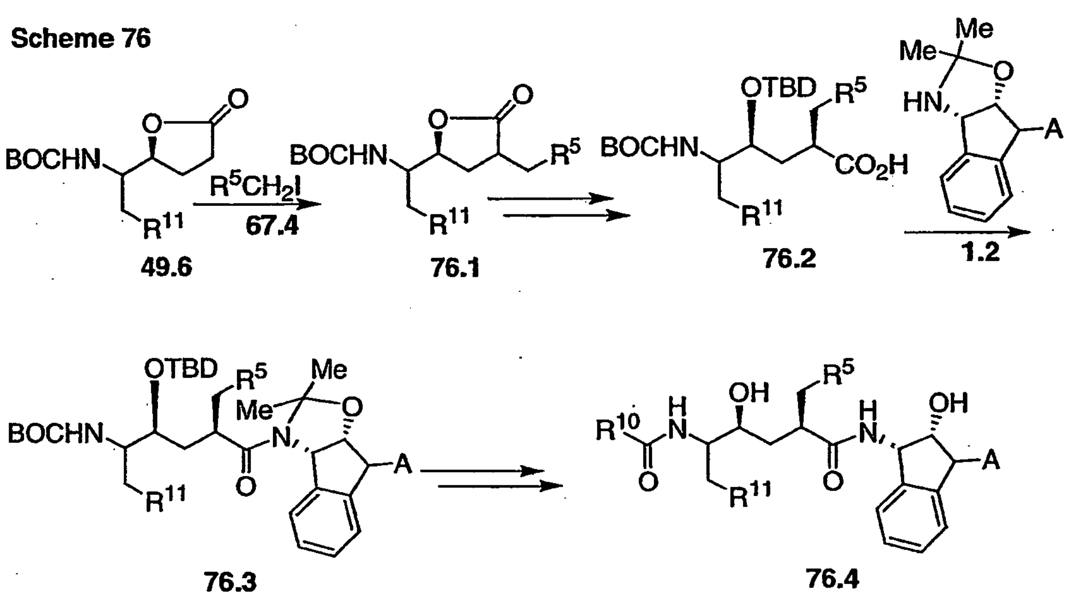
Scheme 74



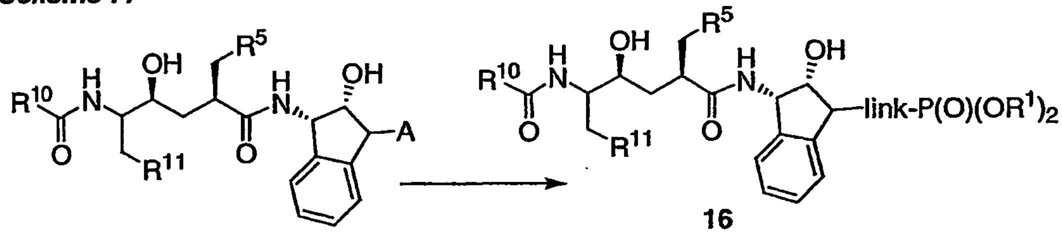
Scheme 75



Scheme 76

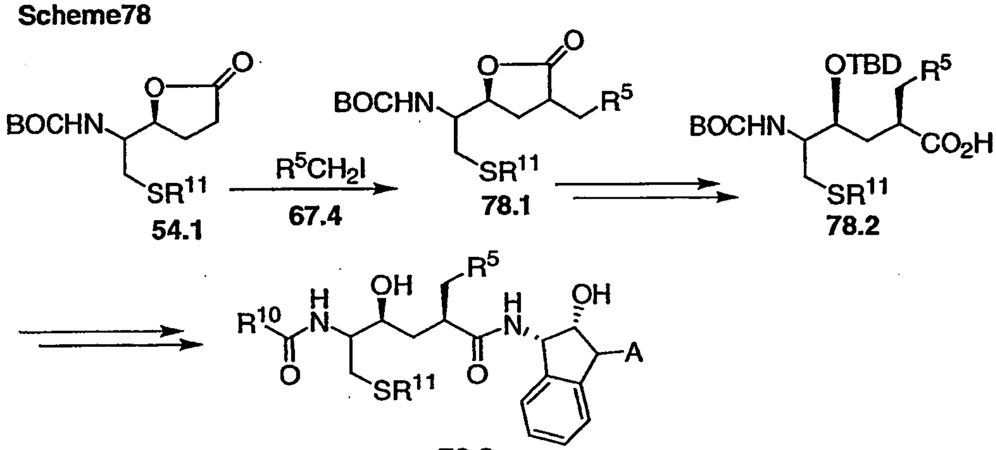


Scheme 77



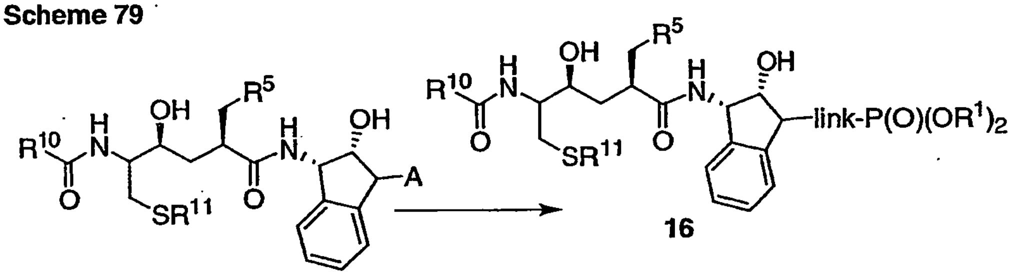
76.4

Scheme78



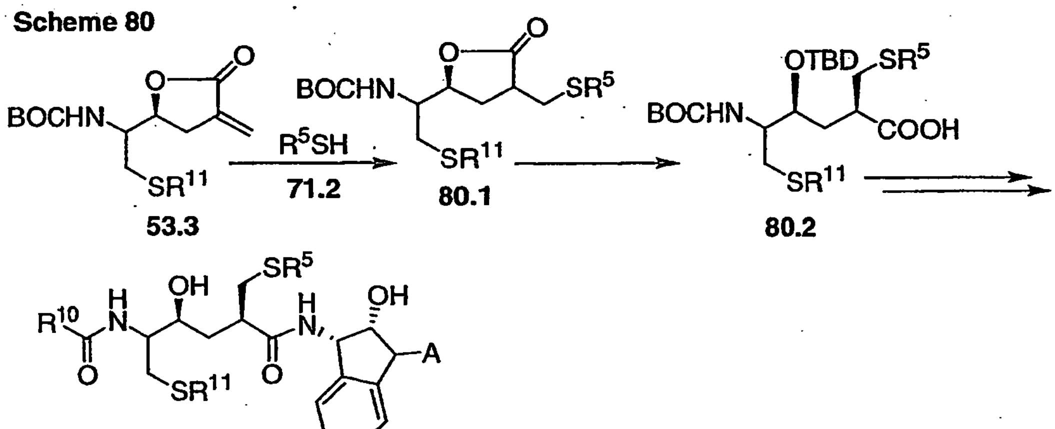
78.3

Scheme 79



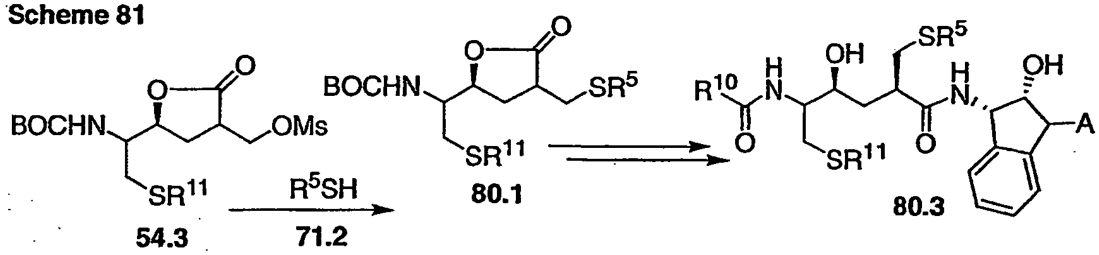
78.3

Scheme 80

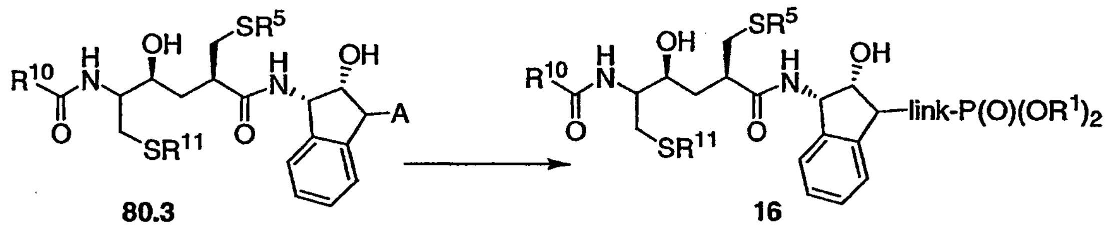


80.3

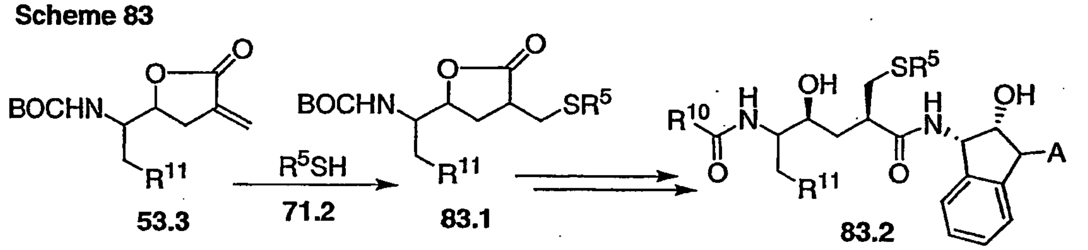
Scheme 81



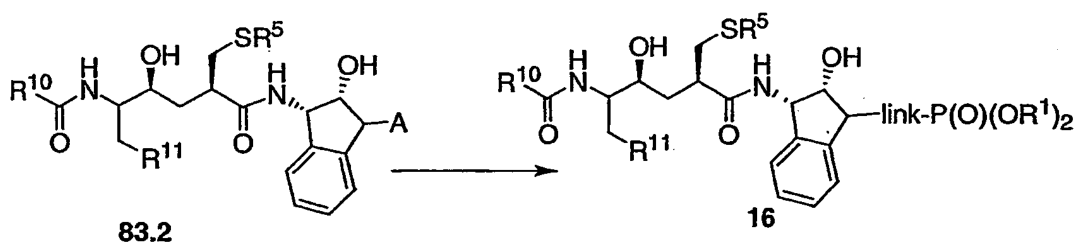
Scheme 82



Scheme 83



Scheme 84



Preparation of the phosphonate ester intermediates 17 in which X and X' are direct bonds.

Schemes **85** and **86** illustrate the preparation of the phosphonate esters **17** in which X and X' are direct bonds. In this procedure, the carboxylic acid **76.2** is coupled, as described in Scheme **1**, with the aminochroman derivative **33.1** to afford the amide **85.1**. The product is then converted, as described in Scheme **49**, into the diamide **85.2**.

The reactions shown in Scheme **85** illustrate the preparation of the compounds **85.2** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **86** depicts the conversion of the compounds **85.2** in which A is [OH], [SH],

[NH], Br, into the phosphonate esters **17** in which X and X' are direct bonds. In this procedure, the compounds **85.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **17**.

Preparation of the phosphonate ester intermediates 17 in which X is a direct bond and X' is sulfur.

Schemes **87** and **88** illustrate the preparation of the phosphonate esters **17** in which X is a direct bond and X' is sulfur. In this procedure, the carboxylic acid **78.2** is coupled with the amine **33.1** to afford the amide **87.1**. The product is then converted, as described in Scheme **49**, into the diamide **87.2**.

The reactions shown in Scheme **87** illustrate the preparation of the compounds **87.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **88** depicts the conversion of the compounds **87.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **17** in which X is a direct bond and X' is sulfur. In this procedure, the compounds **87.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **17**.

Preparation of the phosphonate ester intermediates 17 in which X and X' are sulfur.

Schemes **89** and **90** illustrate the preparation of the phosphonate esters **17** in which X and X' are sulfur. As shown in Scheme **89**, the carboxylic acid **80.2** is coupled, as described in Scheme **1**, with the chroman amine **33.1** to give the amide **89.1**. The product is then transformed, as described in Scheme **49**, into the diamide **89.2**.

The reactions shown in Scheme **89** illustrate the preparation of the compounds **89.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **90** depicts the conversion of the compounds **89.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **17** in which X and X' are sulfur. In this procedure, the compounds **89.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **17**.

Preparation of the phosphonate ester intermediates 17 in which X is sulfur and X' is a direct bond.

Schemes **91** and **92** illustrate the preparation of the phosphonate esters **17** in which X is sulfur and X' is a direct bond. In this procedure, the carboxylic acid **91.1**, which is an intermediate compound in the conversion of the lactone **83.1** into the diamide **83.2**, (Scheme **83**), is coupled, as described in Scheme **1**, with the chroman amine **33.1** to afford the amide **91.2**. The product is then converted, as described in Scheme **49**, into the diamide **91.3**.

The reactions shown in Scheme **91** illustrate the preparation of the compounds **91.3** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **92** depicts the conversion of the compounds **91.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **17** in which X is sulfur and X' is a direct bond. In this procedure, the compounds **91.3** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **17**.

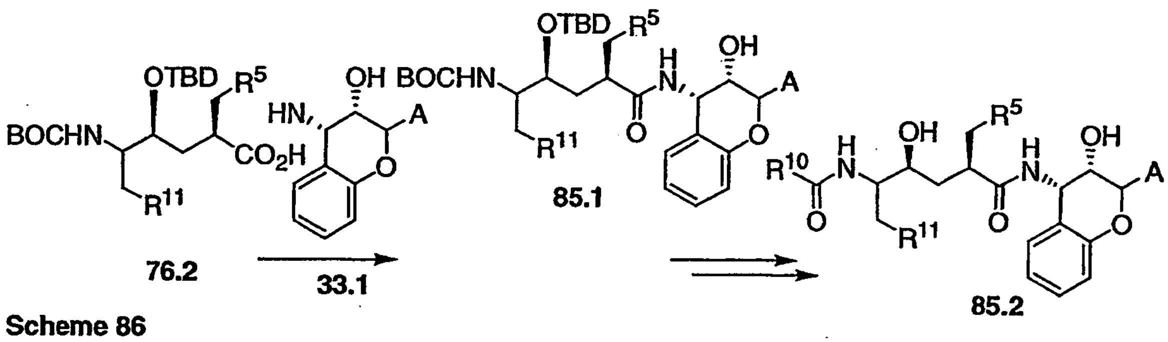
Preparation of the phosphonate ester intermediates 18 in which X and X' are direct bonds.

Schemes **93** and **94** illustrate the preparation of the phosphonate esters **18** in which X and X' are direct bonds. In this procedure, the carboxylic acid **76.2** is coupled, as described in Scheme **1**, with the ethanolamine derivative **29.1** to afford the amide **93.1**. The product is then converted, as described in Scheme **49**, into the diamide **93.2**.

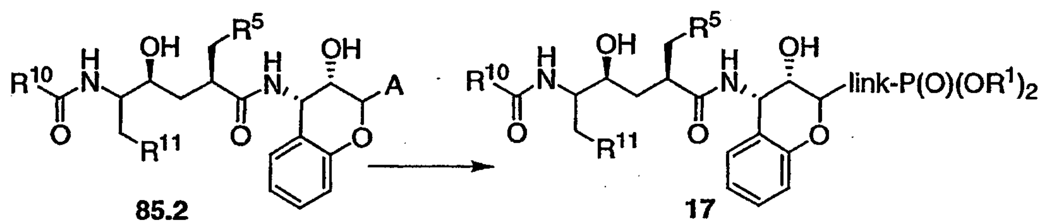
The reactions shown in Scheme **93** illustrate the preparation of the compounds **93.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **94** depicts the conversion of the compounds **93.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **18** in which X and X' are direct bonds. In this procedure, the compounds **93.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **18**.

Preparation of the phosphonate ester intermediates 18 in which X and X' are sulfur.

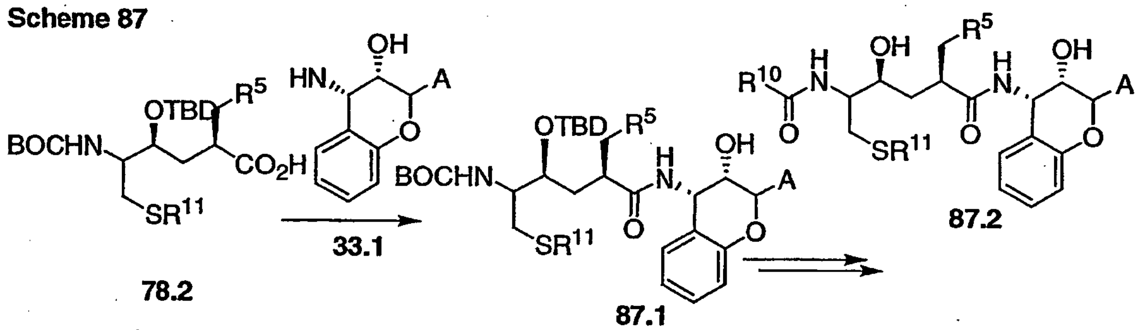
Scheme 85



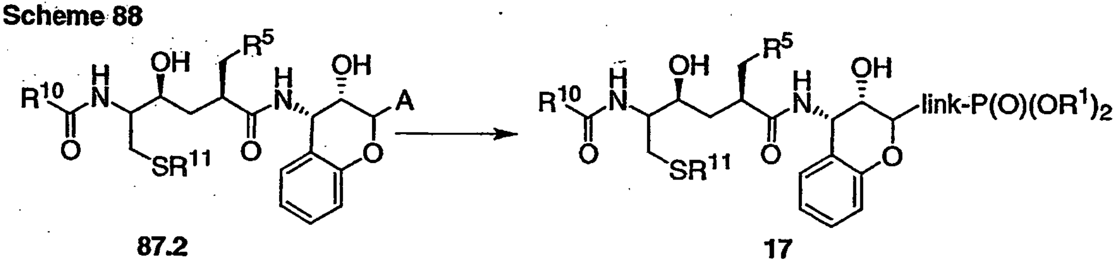
Scheme 86



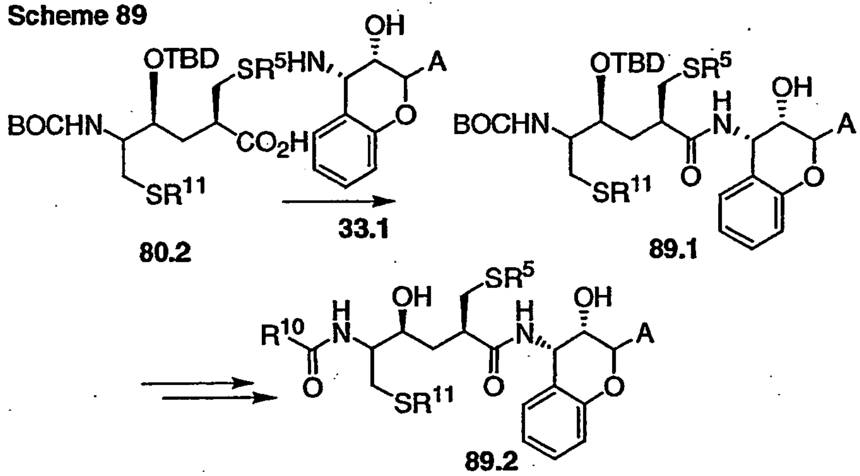
Scheme 87



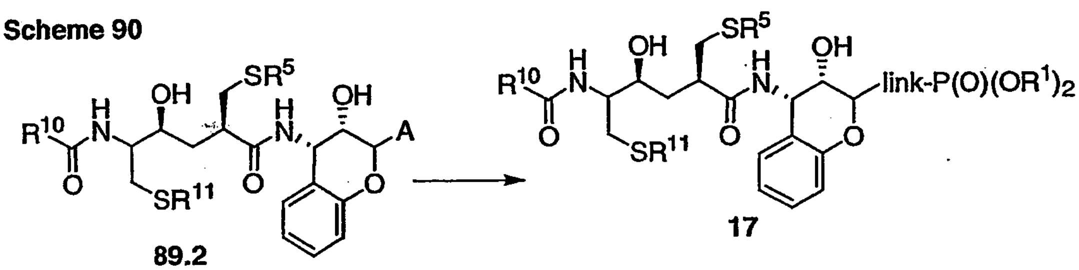
Scheme 88



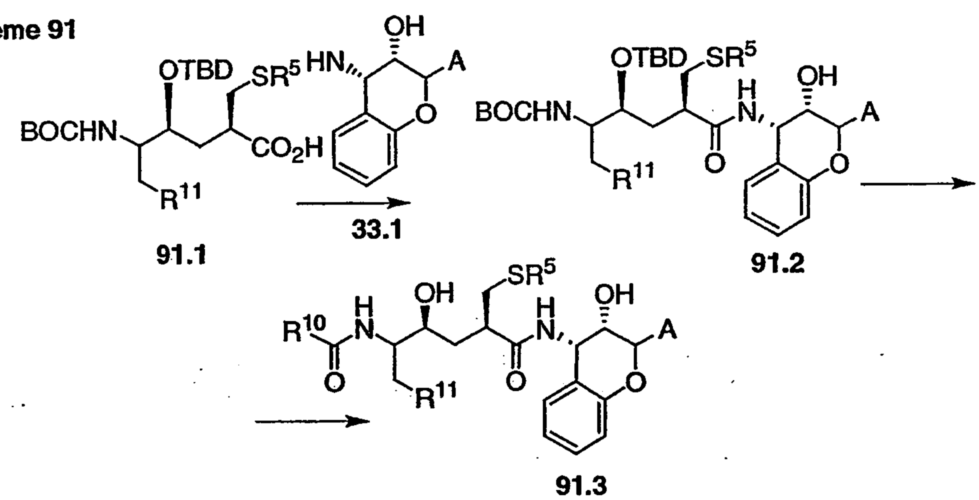
Scheme 89



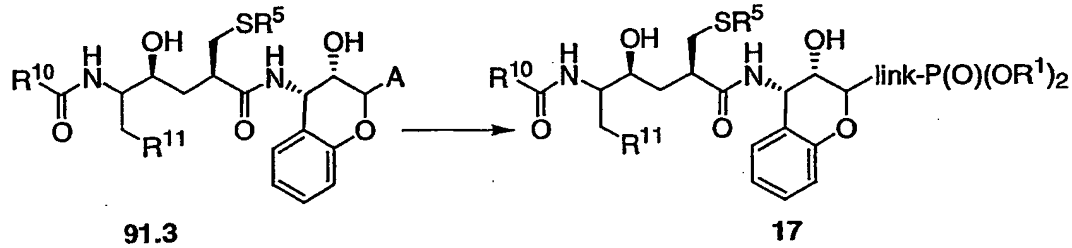
Scheme 90



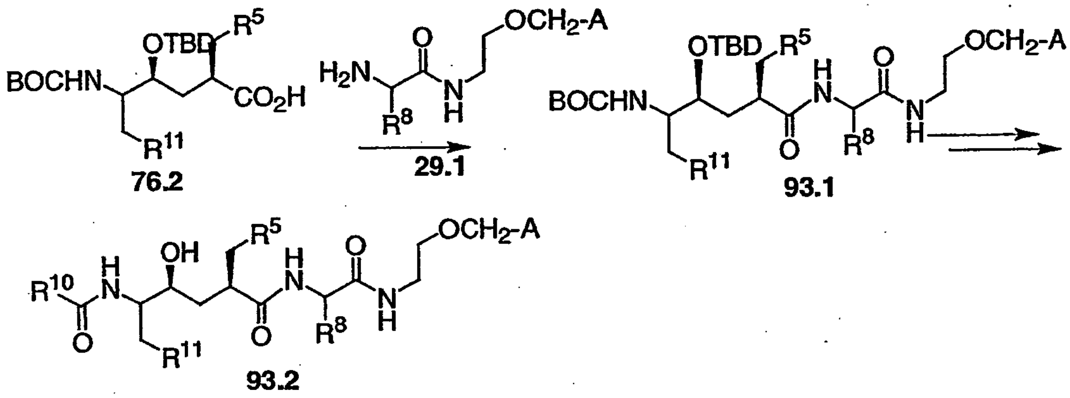
Scheme 91



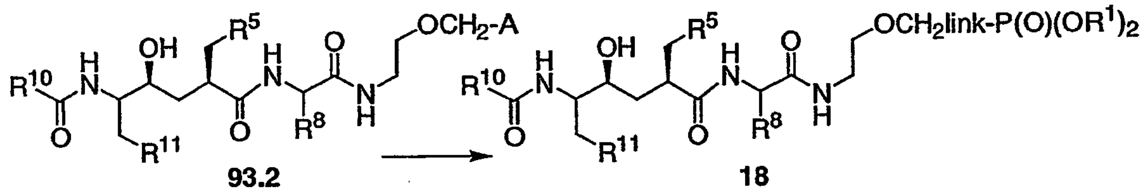
Scheme 92



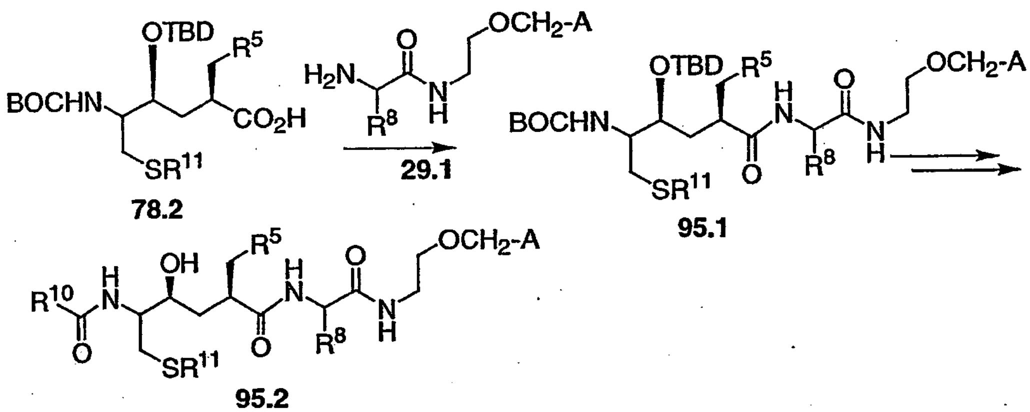
Scheme 93



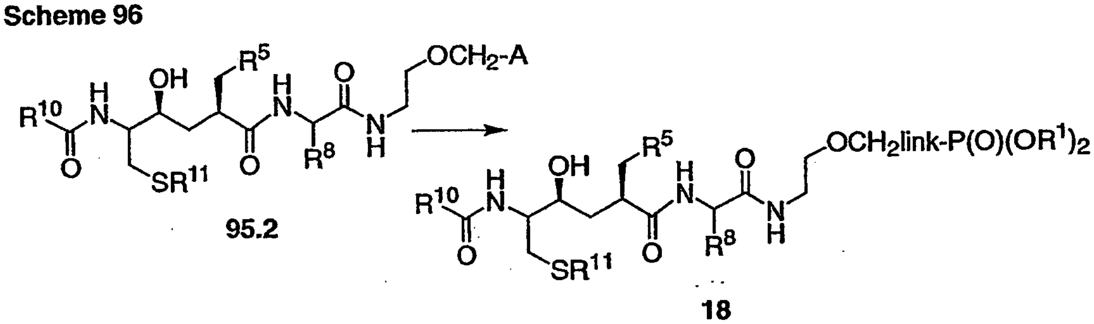
Scheme 94



Scheme 95



Scheme 96



Schemes **97** and **98** illustrate the preparation of the phosphonate esters **18** in which X and X' are sulfur. As shown in Scheme **97**, the carboxylic acid **80.2** is coupled, as described in Scheme **1**, with the ethanolamine derivative **29.1** to give the amide **97.1**. The product is then transformed, as described in Scheme **49**, into the diamide **97.2**.

The reactions shown in Scheme **97** illustrate the preparation of the compounds **97.2** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **98** depicts the conversion of the compounds **97.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **18** in which X and X' are sulfur. In this procedure, the compounds **97.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **18**.

Preparation of the phosphonate ester intermediates 18 in which X is sulfur and X' is a direct bond.

Schemes **99** and **100** illustrate the preparation of the phosphonate esters **18** in which X is sulfur and X' is a direct bond. In this procedure, the carboxylic acid **91.1** is coupled, as described in Scheme **1**, with the ethanolamine derivative **29.1** to afford the amide **99.1**. The product is then converted, as described in Scheme **49**, into the diamide **99.2**.

The reactions shown in Scheme **99** illustrate the preparation of the compounds **99.2** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **100** depicts the conversion of the compounds **99.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **18** in which X is sulfur and X' is a direct bond. In this procedure, the compounds **99.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **18**.

Preparation of the phosphonate ester intermediates 19 in which X and X' are direct bonds.

Schemes **101** and **102** illustrate the preparation of the phosphonate esters **19** in which X and X' are direct bonds. In this procedure, the carboxylic acid **76.2** is coupled, as described in

Scheme **1**, with the phenylalanine derivative **37.1** to afford the amide **101.1**. The product is then converted, as described in Scheme **49**, into the diamide **101.2.**

The reactions shown in Scheme **101** illustrate the preparation of the compounds **101.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **102** depicts the conversion of the compounds **101.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **19** in which X and X' are direct bonds. In this procedure, the compounds **101.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **19.**

Preparation of the phosphonate ester intermediates 19 in which X is a direct bond and X' is sulfur.

Schemes **103** and **104** illustrate the preparation of the phosphonate esters **19** in which X is a direct bond and X' is sulfur. In this procedure, the carboxylic acid **78.2** is coupled, as described in Scheme **1**, with the amine **37.1** to afford the amide **103.1**. The product is then converted, as described in Scheme **49**, into the diamide **103.2.**

The reactions shown in Scheme **103** illustrate the preparation of the compounds **103.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **104** depicts the conversion of the compounds **103.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **19** in which X is a direct bond and X' is sulfur. In this procedure, the compounds **103.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **19.**

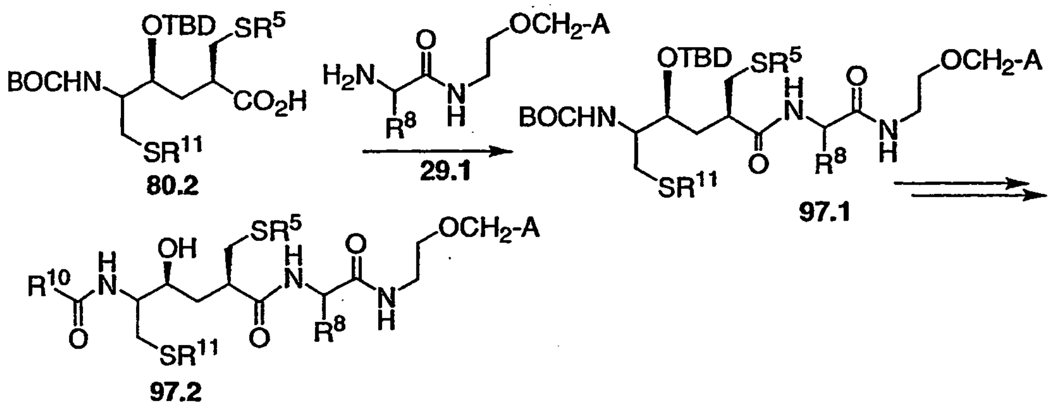
Preparation of the phosphonate ester intermediates 19 in which X and X' are sulfur.

Schemes **105** and **106** illustrate the preparation of the phosphonate esters **19** in which X and X' are sulfur. As shown in Scheme **105**, the carboxylic acid **80.2** is coupled, as described in Scheme **1**, with the phenylalanine derivative **37.1** to give the amide **105.1**. The product is then transformed, as described in Scheme **49**, into the diamide **105.2.**

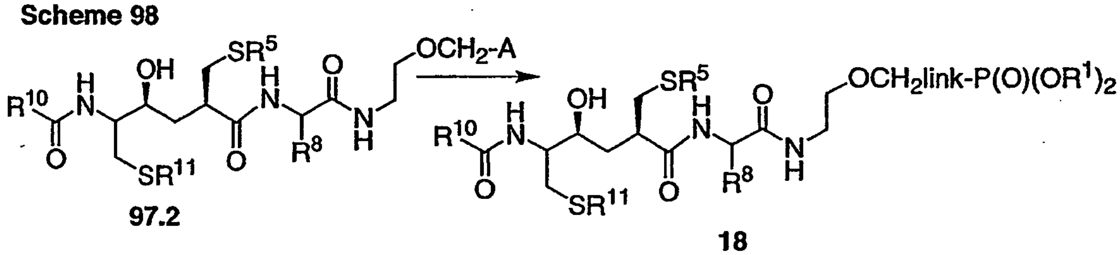
The reactions shown in Scheme **105** illustrate the preparation of the compounds **105.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH],

[SH], [NH], Br. Scheme **106** depicts the conversion of the compounds **105.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **19** in which X and X' are sulfur. In this procedure, the compounds **105.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **19**.

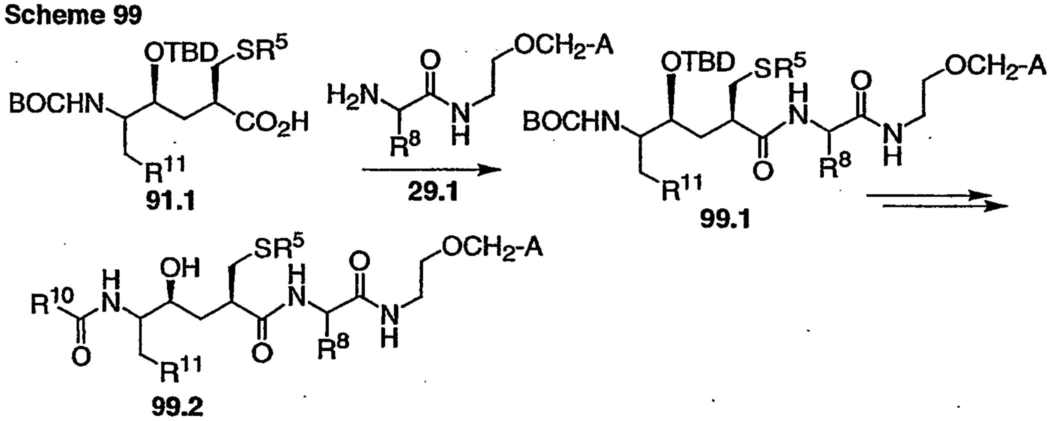
Scheme 97



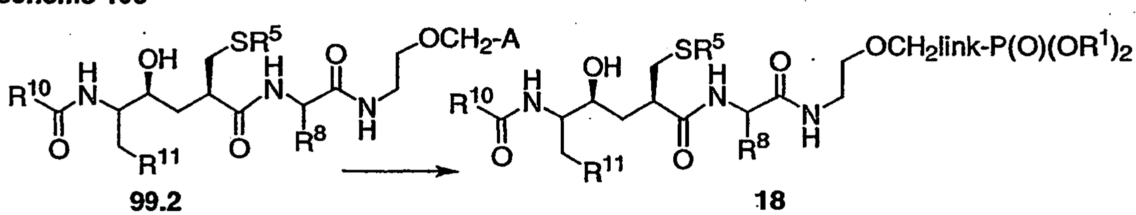
Scheme 98



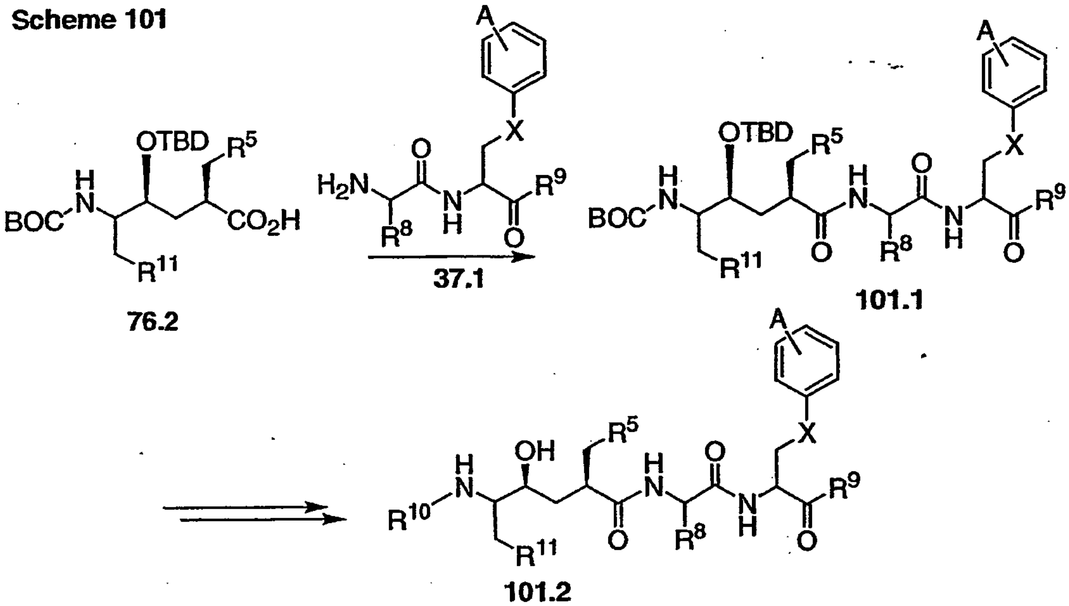
Scheme 99



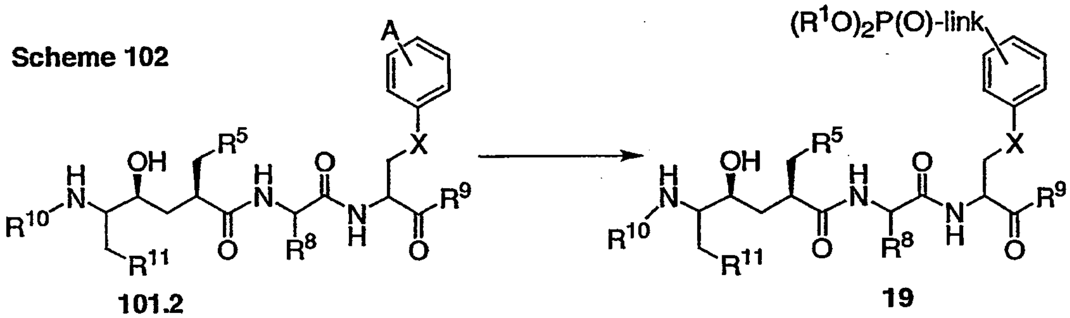
Scheme 100



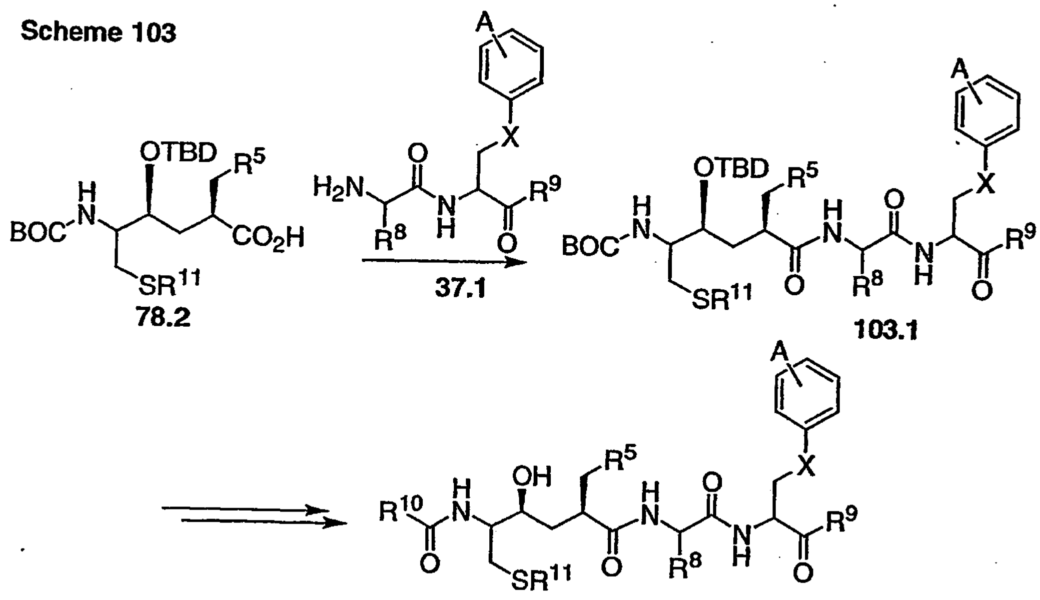
Scheme 101



Scheme 102

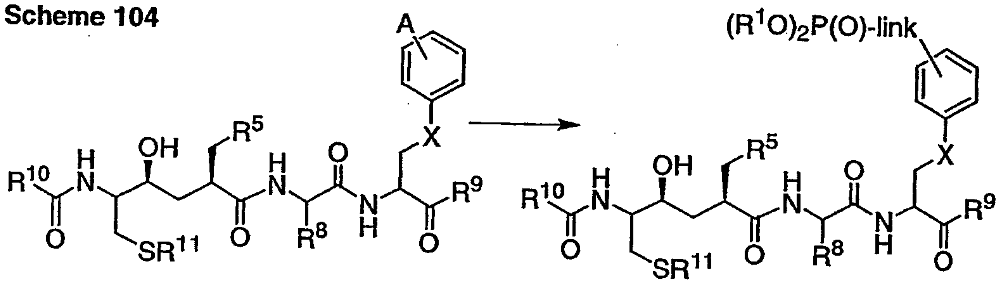


Scheme 103



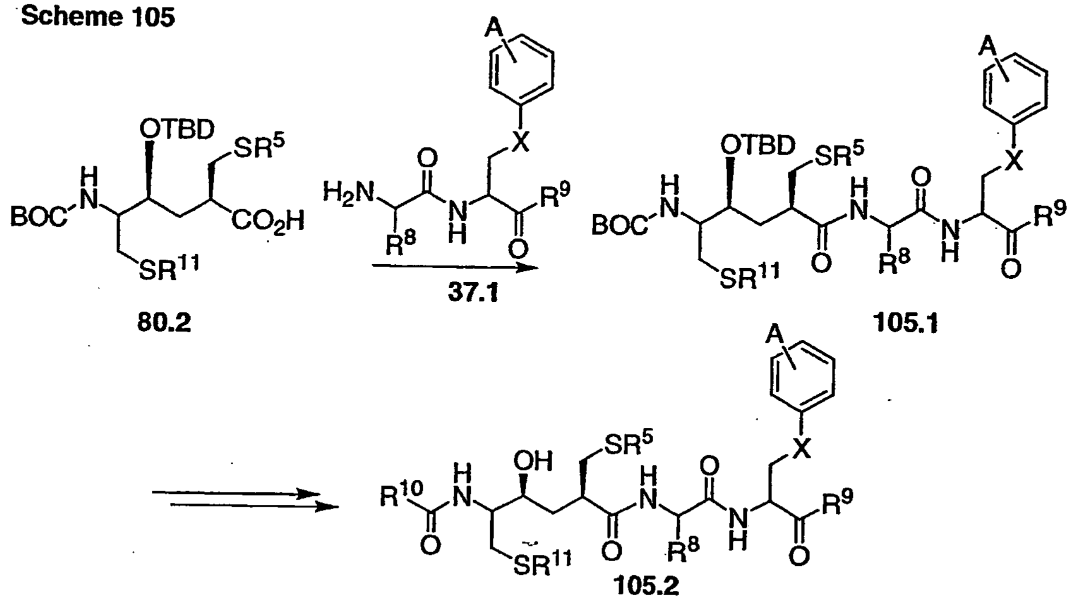
78.2, 37.1, 103.1, 103.2

Scheme 104

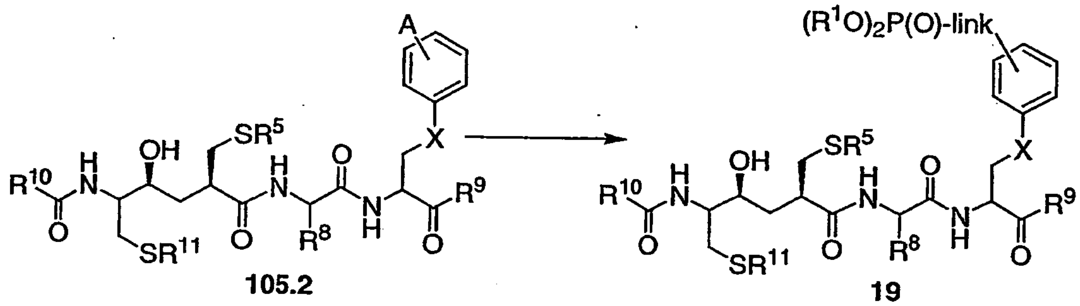


103.2, 19

Scheme 105



Scheme 106



Preparation of the phosphonate ester intermediates 19 in which X is sulfur and X' is a direct bond.

Schemes **107** and **108** illustrate the preparation of the phosphonate esters **19** in which X is sulfur and X' is a direct bond. In this procedure, the carboxylic acid **91.1** is coupled, as described in Scheme **1**, with the phenylalanine derivative **37.1** to afford the amide **107.1**. The product is then converted, as described in Scheme **49**, into the diamide **107.2**.

The reactions shown in Scheme **107** illustrate the preparation of the compounds **107.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **108** depicts the conversion of the compounds **107.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **19** in which X is sulfur and X' is a direct

bond. In this procedure, the compounds **107.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **19**.

Preparation of the phosphonate ester intermediates 20 in which X and X' are direct bonds.

Schemes **109** and **110** illustrate the preparation of the phosphonate esters **20** in which X and X' are direct bonds. In this procedure, the carboxylic acid **76.2** is coupled, as described in Scheme **1**, with the tert. butylamine derivative **41.1** to afford the amide **109.1**. The product is then converted, as described in Scheme **49**, into the diamide **109.2**.

The reactions shown in Scheme **109** illustrate the preparation of the compounds **109.2** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **110** depicts the conversion of the compounds **109.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **20** in which X and X' are direct bonds. In this procedure, the compounds **109.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **20**.

Preparation of the phosphonate ester intermediates 20 in which X is a direct bond and X' is sulfur.

Schemes **111** and **112** illustrate the preparation of the phosphonate esters **20** in which X is a direct bond and X' is sulfur. In this procedure, the carboxylic acid **78.2** is coupled, as described in Scheme **1**, with the amine **41.1** to afford the amide **111.1**. The product is then converted, as described in Scheme **49**, into the diamide **111.2**.

The reactions shown in Scheme **111** illustrate the preparation of the compounds **111.2** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **112** depicts the conversion of the compounds **111.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **20** in which X is a direct bond and X' is sulfur. In this procedure, the compounds **111.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **20**.

Preparation of the phosphonate ester intermediates 20 in which X and X' are sulfur.

Schemes **113** and **114** illustrate the preparation of the phosphonate esters **20** in which X and X' are sulfur. As shown in Scheme **113**, the carboxylic acid **80.2** is coupled, as described in Scheme **1**, with the tert. butylamine derivative **41.1** to give the amide **113.1**. The product is then transformed, as described in Scheme **49**, into the diamide **113.2**.

The reactions shown in Scheme **113** illustrate the preparation of the compounds **113.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **114** depicts the conversion of the compounds **113.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **20** in which X and X' are sulfur. In this procedure, the compounds **113.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **20**.

Preparation of the phosphonate ester intermediates 20 in which X is sulfur and X' is a direct bond.

Schemes **115** and **116** illustrate the preparation of the phosphonate esters **20** in which X is sulfur and X' is a direct bond. In this procedure, the carboxylic acid **91.1** is coupled, as described in Scheme **1**, with the tert. butylamine derivative **41.1** to afford the amide **115.1**. The product is then converted, as described in Scheme **49**, into the diamide **115.2**.

The reactions shown in Scheme **115** illustrate the preparation of the compounds **115.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **116** depicts the conversion of the compounds **115.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **20** in which X is sulfur and X' is a direct bond. In this procedure, the compounds **115.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **20**.

Preparation of the phosphonate ester intermediates 21 in which X and X' are direct bonds.

Schemes **117** and **118** illustrate the preparation of the phosphonate esters **21** in which X and X' are direct bonds. In this procedure, the carboxylic acid **76.2** is coupled, as described in Scheme **1**, with the decahydroisoquinoline derivative **45.1** to afford the amide **117.1**. The product is then converted, as described in Scheme **49**, into the diamide **117.2**.

The reactions shown in Scheme **117** illustrate the preparation of the compounds **117.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **118** depicts the conversion of the compounds **117.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **21** in which X and X' are direct bonds. In this procedure, the compounds **117.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **21**.

Preparation of the phosphonate ester intermediates 21 in which X is a direct bond and X' is sulfur.

Schemes **119** and **120** illustrate the preparation of the phosphonate esters **21** in which X is a direct bond and X' is sulfur. In this procedure, the carboxylic acid **78.2** is coupled, as described in Scheme **1**, with the amine **45.1** to afford the amide **119.1**. The product is then converted, as described in Scheme **49**, into the diamide **119.2**.

The reactions shown in Scheme **119** illustrate the preparation of the compounds **119.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **120** depicts the conversion of the compounds **119.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **21** in which X is a direct bond and X' is sulfur. In this procedure, the compounds **119.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **21**.